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Prefrontal Dopamine D_1 Receptors and Working Memory in Schizophrenia

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Studies in nonhuman primates documented that appropriate stimulation of dopamine (DA) D_1 receptors in the dorsolateral prefrontal cortex (DLPFC) is critical for working memory processing. The defective ability of patients with schizophrenia at working memory tasks is a core feature of this illness. It has been postulated that this impairment relates to a deficiency in mesocortical DA function. In this study, D_1 receptor availability was measured with positron emission tomography and the selective D_1 receptor antagonist [^{11}C]NNC 112 in 16 patients with schizophrenia (seven drug-naive and nine drug-free patients) and 16 matched healthy controls. [^{11}C]NNC 112 binding potential (BP) was significantly elevated in the DLPFC of patients with schizophrenia (1.63 $\pm$ 0.39 ml/gm) compared with control subjects (1.27 $\pm$ 0.44 ml/gm; $p = 0.02$). In patients with schizophrenia, increased DLPFC [^{11}C]NNC 112 BP was a strong predictor of poor performance at the n-back task, a test of working memory. These findings confirm that alteration of DLPFC D_1 receptor transmission is involved in working memory deficits presented by patients with schizophrenia. Increased D_1 receptor availability observed in patients with schizophrenia might represent a compensatory (but ineffective) upregulation secondary to sustained deficiency in mesocortical DA function.

Key words: dopamine; D_1 receptors; schizophrenia; prefrontal cortex; working memory; positron emission tomography

Impairment in higher cognitive functions is one of the most enduring symptoms of schizophrenia and a strong predictor of poor clinical outcome (Green, 1996). Among these deficits, defective performance at tasks involving working memory, i.e., the ability to retain and manipulate information over a brief period of time, has been reliably observed in these patients (Park and Holzman, 1992; Fleming et al., 1995; Morice and Delahunty, 1996; Gold et al., 1997; Keefe et al., 1997; Park, 1997; Conklin et al., 2000). Functional brain imaging studies documented the engagement of the dorsolateral prefrontal cortex (DLPFC) in the execution of working memory tasks in humans (Cohen et al., 1994; McCarthy et al., 1994; Courtney et al., 1996; Braver et al., 1997; Carlson et al., 1998; D'Esposito et al., 1998; Callicott et al., 1999; Jansma et al., 2000). Alterations in DLPFC activation during completion of working memory tasks has been reported in patients with schizophrenia by numerous investigators, suggesting that pathology of the DLPFC or its connectivity is implicated in working memory deficits in schizophrenia (Callicott et al., 1998, 2000; Stevens et al., 1998; Honey et al., 1999; Manoach et al., 1999, 2000; Barch et al., 2001; Perlstein et al., 2001).

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The mesocortical DA system, ascending form the ventral tegmental area, provides a widespread innervation to the neocortical areas (Levitt et al., 1984; Lewis et al., 1987; Oades and Halliday, 1987). D_1 receptors are the most expressed DA receptors in the neocortex (Lidow et al., 1991; Hall et al., 1994; Hurd et al., 2001). Studies in nonhuman primates have shown that working memory, studied during delayed response paradigms, is critically dependent on prefrontal DA function and appropriate stimulation of D_1 receptors in the DLPFC (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991, 1994; Arnsten et al., 1994; Arnsten and Goldman-Rakic, 1998). These observations led to the suggestion that altered DA transmission at D_1 receptors in DLPFC might be involved in the pathophysiology of working memory in schizophrenia (Weinberger, 1987; Davis et al., 1991; Goldman-Rakic, 1994; Goldman-Rakic et al., 2000).

The aim of the study reported here was to measure DLPFC D_1 receptor availability in untreated patients with schizophrenia and matched healthy controls and to assess the relationship between DLPFC D_1 receptor availability and working memory performance. (+)-5-(7-Benzofuranyl)-8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (NNC 112) is a potent and selective D_1 receptor antagonist (Andersen et al., 1992). [^{11}C]NNC 112 was recently introduced as a new and superior radiotracer to image D_1 receptors (Halldin et al., 1998). Because of its high specific to nonspecific binding ratio, [^{11}C]NNC 112 is well suited for quantification of D_1 receptors in extrastriatal areas such as the neocortex (Halldin et al., 1998), where the density of these receptors is much lower than in the striatum (Hall et al., 1994). We recently demonstrated that [^{11}C]NNC 112 provides a reproducible measurement of D_1 receptor parameters in several regions of the PFC, including the DLPFC (Abi-Dargham et al., 2000). Working memory was assessed in both patients and con-

trols, using a verbal n-back paradigm and three working memory load levels (1-back, 2-back, 3-back).

MATERIALS AND METHODS

Subjects

The protocol was approved by the Institutional Review Boards of the New York State Psychiatric Institute and Columbia Presbyterian Medical Center. Patients were recruited after voluntary admission to a research ward (Schizophrenia Research Unit, New York State Psychiatric Institute) or from the affiliated outpatient research clinic. Capacity to provide informed consent was evaluated by a psychiatrist not associated with the study. Subjects provided written informed consent after detailed explanation of the nature and risks of the study. According to the recommendations of the National Alliance for the Mentally Ill (Arlington, VA), assent from involved family members was also obtained when appropriate.

Inclusion criteria for patients were as follows: (1) diagnosis of schizophrenia or schizophreniform disorder (provisional) according to the Diagnostic and Statistical Manual (DSM-IV); (2) no other DSM-IV axis I diagnosis; (3) no lifetime history of alcohol or substance abuse or dependence; (4) absence of any psychotropic medication for at least 14 d before the study (with the exception of lorazepam, which was allowed at a maximal dose of 3 mg per day up to 24 hr before the study); (5) no concomitant or past severe medical conditions; (6) no pregnancy; (7) no current suicidal or homicidal ideation; and (8) capacity to provide informed consent. Subjects with schizophreniform disorder (provisional) were included in the study only if the diagnosis of schizophrenia was confirmed after 6 months.

Inclusion criteria for the control group were (1) absence of past or present neurological or psychiatric illnesses, including substance abuse; (2) no concomitant or past severe medical conditions; (3) no pregnancy; and (4) informed consent. Groups were matched for age, gender, race, parental socioeconomic level (Hollingshead, 1975), and nicotine smoking.

A total of 17 patients with schizophrenia and 20 controls were enrolled in the study. All sequentially enrolled subjects were included in the study sample, with the following exceptions. One patient with schizophrenia was excluded because of failure of arterial sampling during the scan. Three controls subjects were excluded for the following reasons: failure to obtain magnetic resonance image (MRI) ($n = 1$), discovery of a meningioma at the MRI ($n = 1$), and technical failure of the PET scanner during the experiment ($n = 2$). Thus, the final sample includes 16 patients with schizophrenia and 16 healthy controls. Patients and controls were studied over a 2 year period (June 1999 to June 2001).

Clinical assessment

Diagnosis was assessed with the Structured Clinical Interview for DSM-IV (SCID) (Spitzer et al., 1992), followed by consensus diagnosis conference. For controls, a trained rater administered the SCID nonpatient version (SCID-NP). Medical evaluation included a detailed medical and neurological history, complete physical and neurological examination, EKG, and routine laboratory tests. Severity of symptoms was assessed with the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987), obtained on the day of the PET study, i.e., after at least 14 d without antipsychotic medications.

Working memory assessment

A large number of tasks involving working memory have been used in schizophrenia research (Goldman-Rakic, 1994). These tasks might vary in complexity, from pure maintenance tasks (allowing to vary the delay and the extent of information to be maintained) to tasks involving increasing levels of information manipulation (ranging from simple matching to more elaborate decision making processes, such as set shifting in the Wisconsin card sorting task). We selected the n-back paradigm because: (1) it is a reliable method to activate DLPFC, irrespective of the presentation modality or the nature of the information, (2) it allows to vary the working memory load of the task, and (3) DLPFC activation during n-back tasks has been demonstrated to be load-sensitive by several investigators (Cohen et al., 1994; Barch et al., 1997; Braver et al., 1997; Carlson et al., 1998; Carter et al., 1998; Callicott et al., 1999; Rama et al., 2001).

The n-back task used here required subjects to monitor a series of letters presented sequentially on a computer screen and to respond when a letter is identical to the one that immediately preceded it (1-back condition), the one presented two trials back (2-back), or three trials back (3-back) (Cohen et al., 1994). Sixty letters were presented in each condition. Each presentation lasted 500 msec, with 2500 msec intervals (blank screen). A total of 12, 10, and 10 targets were presented for the 1-, 2-, and 3-back conditions, respectively. The hit rate (HR) was calculated as the number of correct responses divided by the number of targets (maximum is 1, minimum is 0). The error rate (ER) was calculated as the number of errors divided by the number of nontargets (maximum is 1, minimum is 0). The adjusted HR (AHR) was calculated as HR − ER. AHR ranges from 1 (if the subject provides all the correct responses and no incorrect response) to −1 (if the subject provides no correct response and all the incorrect responses). Operating at chance level corresponds to an AHR of 0. d′ was calculated for 2 and 3 back as inv(HR) − inv(ER), where inv is the inverse of the standard normal cumulative distribution.

D_1 receptor measurement

Radiochemistry. The desmethyl precursor (+)-5-(7-benzofuranyl)-8-chloro-7-hydroxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine was kindly provided by Christer Halldin (Karolinska Institute, Stockholm, Sweden). [^{11}C]NNC 112 was prepared by *N*-methylation of the precursor using [^{11}C]methyl triflate as previously described (Halldin et al., 1998). Specific radioactivity at the time of injection was 949 ± 533 Ci/mmol (mean ± SD; $n = 32$). Injected dose was 12.5 ± 4.8 mCi, and injected mass was 4.8 ± 1.3 μg (range from 1.8 to 6.5 μg).

PET protocol. PET imaging sessions were conducted as previously described (Abi-Dargham et al., 2000). An arterial catheter was inserted in the radial artery after completion of the Allen test and infiltration of the skin with 2% lidocaine. A venous catheter was inserted in a forearm vein on the opposite side. A polyurethane head immobilizer system (Soule Medical, Tampa, FL) was used to minimize head movement (Mawlawi et al., 1999). PET imaging was performed with the ECAT EXACT HR+ (Siemens, Knoxville, TN) [63 slices covering an axial field of view of 15.5 cm, axial sampling of 2.46 mm, in-plane and axial resolution of 4.4 and 4.1 mm full width half-maximum at the center of the field of view in the three-dimensional mode (3-D), respectively]. A 10 min transmission scan was obtained before radiotracer injection. [^{11}C]NNC 112 was injected intravenously over a 45 sec period. Emission data were collected in the 3-D mode for 90 min as 18 successive frames of increasing duration (3 × 20 sec, 3 × 1 min, 3 × 2 min, 2 × 5 min, 7 × 10 min). Images were reconstructed with attenuation correction using the transmission data and a Sheppe 0.5 filter (cutoff 0.5 cycles per projection rays).

Input function measurement. After radiotracer injection, arterial samples were collected every 10 sec with an automated sampling system for the first 2 min, and manually thereafter at longer intervals. A total of 30 samples was obtained per experiment. After centrifugation (10 min at 1800 × *g*), a 200 μl aliquot of plasma was collected, and activity was measured in a gamma counter (1480 Wizard 3M automatic gamma counter; LKB-Wallac, Gaithersburg, MD). Gamma counter efficiency was calibrated at regular intervals with the PET camera using an ^{18}F solution. In addition, a long-lived source (^{22}Na) was counted with each set of samples, to control for between run variance in counting efficiency. Six selected samples (collected at 2, 8, 16, 30, 50, and 70 min) were further processed by protein precipitation using acetonitrile followed by HPLC to measure the fraction of plasma activity representing unmetabolized parent compound, as previously described (Abi-Dargham et al., 2000).

A biexponential function was fitted to the six measured fractions parent and used to interpolate values between and after the measurements. The smallest exponential of the fraction parent curve, λ_{par}, was constrained to the difference between λ_{cer}, the terminal rate of washout of cerebellar activity, and λ_{tot}, the smallest elimination rate constant of the total plasma (Abi-Dargham et al., 1999). The input function was calculated by the product of total counts and interpolated fraction parent at each time. The measured input function values ($C_a(t)$, μCi/ml) were fitted to a sum of three exponentials, and the fitted values were used as input to the kinetic analysis of the regional brain uptake. The clearance of the parent compound (C_L, l/hr) was calculated as the ratio of the injected dose to the area under the curve of the input function (Abi-Dargham et al., 1994).

For the determination of the plasma-free fraction (f_1), triplicate 200 μl aliquots of plasma collected before injection were mixed with radiotracer, pipetted into ultrafiltration units (Centrifree; Amicon, Danvers, MA), and centrifuged at room temperature (20 min at 4000 rpm). At end of centrifugation, plasma and ultrafiltrate activities were counted, and f_1

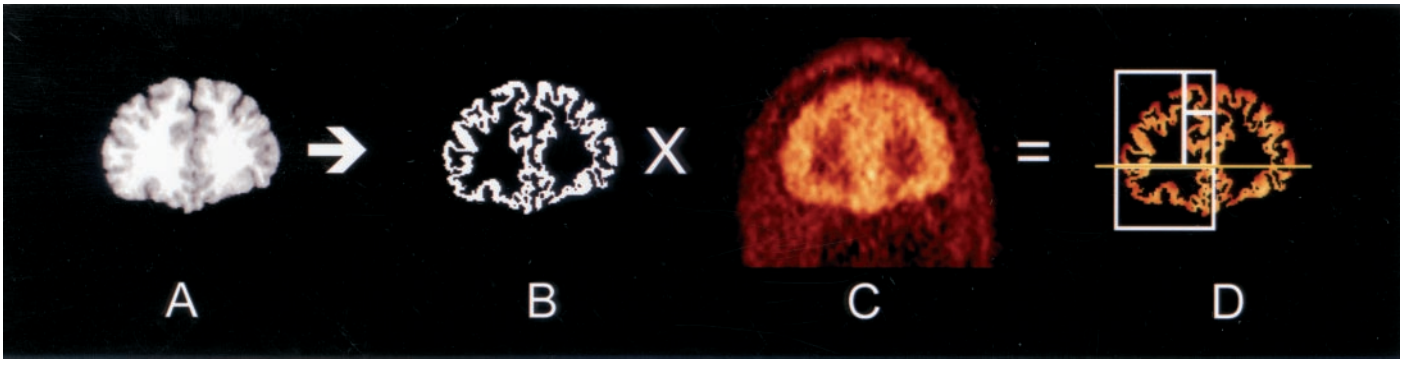

Figure 1. Illustration of the steps involved in the sampling of activity from cortical regions. A coronal section 0.5 mm anterior to the rostral part of the corpus callosum is displayed. The MRI (*A*) is segmented into white matter, gray matter, and CSF voxels. Gray matter voxels are assigned a value of 1, and all other pixels are assigned a value of 0 to form a gray inverted mask image (*B*). The coregistered PET image (*C*) is multiplied by the mask (*B*) to form a gray matter PET image (*D*). Regional activities are sampled on *D* in nonzero voxels. Region boundaries (*white lines*) are illustrated on the *right*. The *yellow line* corresponds to the AC–PC plane. The region ventral to this plane is the OFC. Regions dorsal to the AC–PC plane are divided into a lateral region (DLPFC) and medial regions, which, at this level, include the MPFC and ACC, dorsal and ventral to the cingulate gyrus, respectively.

was calculated as the ratio of ultrafiltrate to total activity concentrations (Gandelman et al., 1994).

MRI acquisition and segmentation procedures. MRIs were acquired on a GE 1.5 T Signa Advantage system. After a sagittal scout (1 min), performed to identify the anterior commissure (AC)–posterior commissure (PC) plane, a transaxial T1-weighted sequence with 1.5 mm slice thickness was acquired in a coronal plane orthogonal to the AC–PC plane over the whole brain with the following parameters: three-dimensional spoiled gradient recalled acquisition in the steady state; repetition time, 34 msec; echo time, 5 msec; flip angle of 45°; slice thickness 1.5 mm and zero gap; 124 slices; field of view, 22 × 16 cm; with 256 × 192 matrix, reformatted to 256 × 256, yielding a voxel size of 1.5 × 0.9 × 0.9 mm; and time of acquisition, 11 min. MRI segmentation was performed within MEDx (Sensor Systems, Inc., Sterling, VA), with original subroutines implemented in MATLAB (Math Works, Natick, MA). Steps for MRI segmentation included correction for field inhomogeneities, fitting of the voxel distribution to a combination of three Gaussian functions, voxel classification, and post filtering (Abi-Dargham et al., 2000).

Image analysis. Image analysis was performed blind to the subject diagnosis with MEDx (Sensor Systems, Inc., Sterling, VA). To correct for head movement during the acquisition, all frames were coregistered to a frame of reference, using a least-square algorithm for within modalities coregistration [automated image registration (AIR)] (Woods et al., 1992). After frame-to-frame registration, the 18 frames were summed, and the summed PET image was coregistered and resampled to the MRI, using AIR (Woods et al., 1993). The summed PET image was used for the coregistration because it contains counts from the initial, flow-dependent, activity distribution, which enhances detection of boundaries of regions with low receptor density, such as the cerebellum. The parameters of the spatial transformation matrix of the summed PET data set were then applied to each individual frame. Thus, each PET frame was resampled in the coronal plane to a voxel volume of $1.5 \times 0.9 \times 0.9\ mm^3$.

The boundaries for 14 regions of interest (ROIs) and one region of reference were drawn on the MRI according to criteria based on brain atlases (Talairach and Tournoux, 1988; Duvernoy, 1991) and on published reports (Pani et al., 1990; Kates et al., 1997; Killiany et al., 1997). Cortical regions ($n = 8$) included DLPFC, medial prefrontal cortex (MPFC), orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), parietal cortex (PC), temporal cortex (TC), parahippocampal gyrus (PHG), and occipital cortex (OC).

The prefrontal cortex was sampled from the most rostral plane to the plane corresponding to the rostral boundary of the genu of the corpus callosum. Prefrontal area ventral to the AC–PC plane was labeled OFC and included the inferior rostral gyrus, the gyrus rectus, the orbital gyrus, and the inferior frontal gyrus (orbital part). Prefrontal area dorsal to the AC–PC plane was divided into a lateral and medial section (medial section defined as cortex adjacent to the interhemispheric fissure). The lateral section (dorsal part of superior frontal gyrus, middle frontal gyrus and inferior frontal gyrus, triangular part) was labeled DLPFC. This region includes Brodmann areas 9 and 46 (Rajkowska and Goldman-Rakic, 1995). The medial section excluded the anterior cingulate and corresponded to the MPFC (areas 8 and 9, medial part of the superior frontal gyrus).

Subcortical regions ($n = 6$) included dorsal caudate (DCA), dorsal putamen (DPU), ventral striatum (VST), thalamus (THA), amygdala (AMY), and hippocampus (HIP). Criteria used to delineate striatal subregions (DCA, DPU, and VST) are found in Mawlawi et al. (2001), and criteria used for other regions are available on request. Right and left regions for bilateral ROIs were averaged. The cerebellum (CER), a region with negligible density of D_1 receptors, was used as region of reference to define the distribution volume of the nonspecific compartment.

Two methods were used for final ROI definition. A segmentation-based method was used for cortical regions, and a direct identification method was used for subcortical regions. For cortical regions, "large" regions were first drawn to delineate the boundaries of the ROIs. Within these regions, only the voxels classified as gray matter voxels by the MRI segmentation procedure were sampled to measure activity distribution (see details in Abi-Dargham et al., 2000). The steps involved in this method are illustrated in Figure 1. Because of the mixture of gray and white matter in central gray structures (especially thalamus), the segmentation-based approach was not used to define subcortical ROIs, and the boundaries of these regions were identified by anatomical criteria. The CER region included the whole structure (both gray and white matter).

Derivation of regional total distribution volumes. Derivation of [^{11}C]NNC 112 regional distribution volumes was performed using kinetic analysis and a three compartment model in the ROIs and a two compartment model in the cerebellum (Mintun et al., 1984; Abi-Dargham et al., 2000). The three compartment configuration included the arterial plasma compartment (C_a), the intracerebral free and nonspecifically bound compartment (nondisplaceable compartment, C_2), and the specifically bound compartment (C_3). Brain activity was corrected for the contribution of plasma activity assuming a 5% blood volume (Mintun et al., 1984).

The total regional distribution volume (V_T, milliliters of plasma per gram of tissue) was defined as the ratio of the tracer concentration in this region (C_T) to the metabolite-corrected plasma concentration at equilibrium:

$$V_T = \frac{C_T}{C_a}. \quad (1)$$

V_T is equal to the sum of the distribution volumes for the second (nondisplaceable, V_2) and third (specific, V_3) compartments. V_T was derived from the kinetic rate constants as:

$$V_T = \frac{K_1}{k_2}\left(1 + \frac{k_3}{k_4}\right), \quad (2)$$

where K_1 (in milliliters per gram per minute) and k_2 (min^{-1}) are the unidirectional fractional rate constants for the transfer between C_a and C_2, and k_3 (min^{-1}) and k_4 (min^{-1}) are the unidirectional fractional rate

constants for the transfer between C_2 and C_3. The terms K_1 and k_2 include the regional blood flow: $K_1 = F(1 - \exp^{PS/F})$ where F is regional blood flow, and PS is the permeability surface area product of the tracer; $k_2 = K_1/V_2f_1$. Thus, distribution volumes (V_2, V_3, and V_T) are flow independent (the flow is present in both numerator and denominator and cancels out).

Kinetic parameters were derived by nonlinear regression using a Levenberg–Marquardt least-squares minimization procedure (Levenberg, 1944) implemented in MATLAB (Math Works) as previously described (Laruelle et al., 1994b). Given the unequal sampling over time (increasing frame acquisition time from beginning to end of the study), the least squares minimization procedure was weighed by the square root of the frame acquisition time.

Derivation of binding potential. The binding potential (BP, milliliters per gram) was derived as the difference between total (V_T) and nonspecific (V_2) distribution volumes, with cerebellum V_T used as a measure of V_2:

$$BP = V_T - V_2. \quad (3)$$

Under these conditions, BP is equal to (Laruelle et al., 1994a):

$$BP = \frac{f_1 B_{max}}{K_D}, \quad (4)$$

where B_{max} is the regional concentration of D_1 receptors, K_D is the affinity of [^{11}C]NNC 112 for D_1 receptors, and f_1 is the free fraction of [^{11}C]NNC 112 in the plasma. Although f_1 was measured in this study, the derivation of BP was not corrected for f_1, given the low free fraction of [^{11}C]NNC 112 in the plasma (<1%) and the lack of reliability of f_1 measurement when f_1 is <10% (Abi-Dargham et al., 2000).

A second outcome measure of interest was the BP normalized to cerebellum distribution volume, termed V_3''. V_3'' is equal to the ratio of BP to V_2 (Laruelle et al., 1994a):

$$V_3'' = \frac{BP}{V_2} = \frac{f_1 B_{max}}{V_2 K_D} = \frac{f_2 B_{max}}{K_D}, \quad (5)$$

where f_2 is the free fraction in the nondisplaceable compartment ($f_2 = f_1/V_2$). Comparing Equations 4 and 5 informs on the nature of BP and V_3'', respectively. Both outcome measures are related to receptor parameters B_{max} and K_D plus a term unrelated to receptor parameters, f_1 and f_2, respectively. Thus, BP corrects for between-subject differences in nonspecific binding in the brain, but is affected by between-subject differences in nonspecific binding in the plasma. V_3'' corrects for between-subject differences in nonspecific binding in the plasma, but is affected by between-subject differences in nonspecific binding in the brain. [^{11}C]NNC 112 test–retest studies demonstrated that BP and V_3'' are affected by similar test–retest variability, but that the intraclass correlation coefficient of BP was superior to V_3'' (Abi-Dargham et al., 2000). Thus, BP as defined by Equation 4 was *a priori* selected as the primary outcome measure for this study.

Statistical analysis

Between-group comparisons were performed using two-tailed unpaired t tests. Relationships between continuous variables were analyzed with the Pearson product moment correlation coefficient. A probability value of 0.05 was selected as significance level.

The primary hypothesis of this study related to DLPFC D_1 receptor, and no correction for multiple testing was applied to this region. Other regions were analyzed and compared between groups, to test the regional specificity of the finding in DLPFC. To correct for multiple testing and explore the covariance structure among regions, principal component analysis with varimax transformation was performed on the complete sample. Individual regional BP values were transformed into z scores and reduced to an appropriate number of factors using the factor weights derived by the principal component analysis. Repeated measure ANOVA was performed with factors as repeated measure and diagnosis as grouping variable to test the existence of a factor by diagnosis interaction, followed by unpaired t test on each factor.

RESULTS

Sample composition

Table 1 lists the demographic and clinical variables of the samples. Groups were matched for age, gender, race, socioeconomic status of the family of origin, and nicotine smoking. The socioeconomic status of patients was lower than controls. In the patient group, seven subjects were experiencing a first episode of illness and had never been treated with antipsychotic medications at the time of the scan. Nine subjects were chronic patients who had been previously treated with antipsychotic drugs. At the time of the scan, these patients were off antipsychotics for 164 ± 173 d (range from 15 to 360 d, with the latter value used for patients off antipsychotic drugs for >1 year). Twelve patients were studied as inpatients, and four patients were studied as outpatients. Duration of illness was 6.8 ± 7.1 years (range from 4 weeks to 26 years). Patients displayed a moderate level of symptom severity. PANSS-positive symptoms subscale (seven positive symptoms rated from 1 to 7) score was 18.6 ± 7.5 (range from 7 to 33). PANSS-negative symptoms subscale (seven negative symptoms rated from 1 to 7) was 18.4 ± 5.7 (range from 11 to 30). PANSS general psychopathology subscale (16 symptoms rated from 1 to 7) was 33.6 ± 7.6 (18–48).

Table 1. Demographic and clinical variables of the samples

Variables	Controls	Patients	p
n	16	16	
Age	34 ± 10	33 ± 12	0.85
Gender (F/M)[a]	5/11	3/13	0.29
Race (C/AA/H/AS)[b]	6/4/5/1	6/4/4/2	0.95
Subject SES[c]	35 ± 16	18 ± 3	<0.01
Family SES	42 ± 13	43 ± 17	0.87
Nicotine smoking (N/Y/E)[d]	9/4/3	12/1/3	0.42
DN/DF[e]		7/9	
Drug-free interval (DF patients)		164 ± 173	
PANSS Positive symptoms subscale		19 ± 7	
PANSS Negative symptoms subscale		18 ± 6	
PANSS General psychopathology subscale		34 ± 7	

[a]F, Female; M, male.

[b]C, Caucasian; AA, African-American; H, Hispanic; AS, Asian.

[c]SES, Socioeconomic status, measured with Hollingshead scale (Hollingshead, 1975).

[d]N, Nonsmoker; Y, currently smoking; E, ex-smoker.

[e]DN, Drug (antipsychotic) naive patient, experiencing a first episode of illness; DF, drug (antipsychotic)-free patients, i.e. patients previously treated with antipsychotic drugs but not currently taking antipsychotic medications for at least 14 d.

Working memory assessment

The n-back task was administered to 14 patients and 15 controls (three subjects were not available for testing). Twelve patients completed the n-back during the drug-free interval preceding the PET study, and two completed it after the PET study, while on antipsychotic medications (for scheduling reasons, not for clinical reasons).

Figure 2 presents the AHR for the 1-, 2-, and 3-back conditions for controls and patients with schizophrenia. Controls performed almost perfectly at the 1- back with an AHR of 0.99 ± 0.03. The AHR in controls decreased to 0.86 ± 0.10 at 2-back and 0.72 ± 0.18 at 3-back. The AHR in patients with schizophrenia was 0.88 ± 0.16 at 1-back, 0.61 ± 0.30 at 2-back, and 0.50 ± 0.28 at 3-back. Each of these distributions had a mean significantly different from zero (one sample t test; $p < 0.001$), indicating that patients performed significantly above chance levels.

The effect of working memory load (1- vs 2- vs 3-back) and diagnosis on the AHR was evaluated with repeated measure

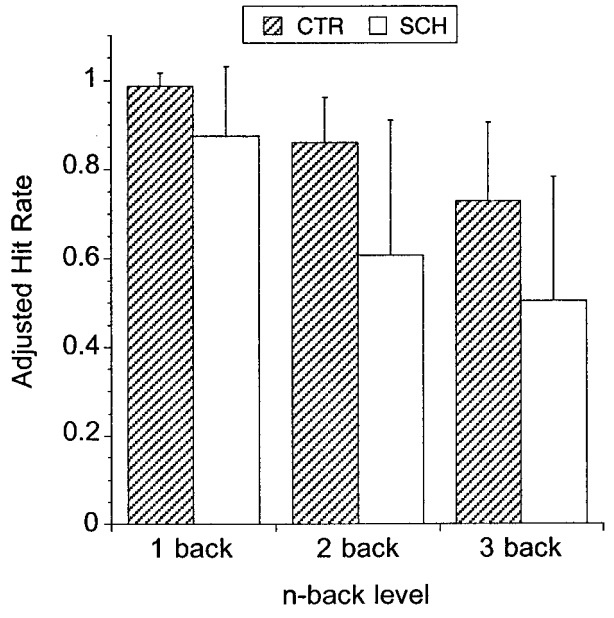

Figure 2. Adjusted hit rate (mean ± SD) for the 1-, 2-, and 3-back conditions in controls (*CTR; n* = 15) and patients with schizophrenia (*SCH; n* = 14). The adjusted hit rate is the hit rate (number of correct responses divided by number of targets) corrected for the error rate (number of incorrect responses divided by number of nontargets) and ranges from +1 to −1. Patients performed significantly worse than controls at each level of the task, but above chance level (score of zero). Increasing task difficulty results in similar relative decrements in performance in patients and controls (repeated measures ANOVA, task level, $p < 0.0001$; diagnosis factor, $p = 0.0017$; diagnosis by task level interaction, $p = 0.27$).

ANOVA, with load level as repeated factor. This test indicated a significant effect of task level ($p < 0.0001$), diagnosis ($p = 0.001$), but no task level by diagnosis interaction ($p = 0.23$). Patients performed worse than controls at each level of the task (1-back, $p = 0.011$; 2-back, $p = 0.005$; 3-back, $p = 0.015$). AHR variance was larger in patients compared with controls at the 1-back ($p < 0.0001$), the 2-back ($p = 0.003$), but not the 3-back ($p = 0.10$). d' was calculated for 2-back and 3-back. For both conditions, d′ in the patient group (2-back d′, 2.07 ± 1.04; 3-back d′, 1.75 ± 1.01) was significantly lower than d′ in the control group (2-back d′, 3.10 ± 0.60, $p = 0.005$; 3-back d′, 2.57 ± 0.75, $p = 0.003$). AHR at 1-, 2-, and 3-back conditions were not associated with age ($r^2 < 0.01$ for all three correlations).

Among patients with schizophrenia, no differences were noted in AHR at any level of the test between first episode patients never previously exposed to antipsychotics ($n = 7$; AHR at 1-, 2-, and 3-back of 0.90 ± 0.10, 0.64 ± 0.28, and 0.49 ± 0.31, respectively) and chronic patients previously treated with antipsychotics ($n = 7$; AHR at 1-, 2-, and 3-back of 0.85 ± 0.20, 0.57 ± 0.33, and 0.52 ± 0.26, respectively). Severity of positive, negative, or general symptoms measured with the PANSS subscales were not predictive of performance at 1-back, 2-back, or 3-back conditions ($r^2 < 0.15$, $p > 0.05$ for all correlations).

D_1 receptor measurements

[^{11}C]NNC 112 injection parameters

No significant between-group differences were observed in the [^{11}C]NNC 112-injected dose (controls: 13.0 ± 4.4 mCi; patients with schizophrenia: 11.9 ± 5.2 mCi; $p = 0.53$), specific activity at time of injection (controls: 1022 ± 545 Ci/mmol; patients with schizophrenia: 876 ± 528 Ci/mmol; $p = 0.44$), or injected mass (controls: 4.7 ± 1.3 μg; patients with schizophrenia: 5.0 ± 1.2 μg; $p = 0.47$).

Table 2. ROI volumes in controls and patients with schizophrenia (cm^3)

Region	Subregion	Controls	Patients
Neocortex	DLPFC	33.2 ± 6.3	35.2 ± 5.8
	MPFC	9.1 ± 2.4	10.8 ± 4.8
	OFC	11.3 ± 4.8	11.8 ± 4.1
	TC	50.8 ± 9.3	54.9 ± 12.1
	PC	61.2 ± 13.1	69.0 ± 13.9
	OC	43.3 ± 7.8	40.0 ± 7.6
Limbic/paralimbic	ACC	6.7 ± 1.6	6.8 ± 1.1
	AMY	3.6 ± 0.4	3.4 ± 0.8
	HIP	7.0 ± 1.2	6.1 ± 1.3
	PHG	11.9 ± 1.5	10.8 ± 1.7
Striatum	DCA	5.2 ± 0.7	5.1 ± 0.7
	DPU	7.8 ± 0.9	8.3 ± 1.1
	VST	2.1 ± 0.9	2.2 ± 0.6
Thalamus		8.3 ± 0.9	7.7 ± 1.3

Values are mean ± SD; $n = 16$ per group. DLPFC, Dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; ACC, anterior cingulate cortex; AMY, amygdala; HIP, hippocampus; PHG, parahippocampal gyrus; DCA, dorsal caudate; DPU, dorsal putamen; VST, ventral striatum. No significant between group differences were observed. HIP and PHG were smaller in patients with schizophrenia at trend level ($p = 0.055$ and 0.068, respectively).

[^{11}C]NNC 112 input function

No significant between-group differences were observed in the clearance rate of [^{11}C]NNC 112 from the plasma compartment (controls: 83 ± 21 l/hr; patients with schizophrenia: 85 ± 32 l/hr; $p = 0.81$). The plasma-free fraction (f_1) was similar in control subjects (0.81 ± 0.34%) and patients with schizophrenia (0.83 ± 0.38%; $p = 0.88$), supporting the use of BP as outcome measure (Eq. 4) for between-group comparisons.

[^{11}C]NNC 112 cerebellum distribution volume

The cerebellum distribution volume (V_2) was derived using a two compartment model and was not significantly different between control subjects (1.92 ± 0.43 ml/gm) and patients with schizophrenia (1.81 ± 0.46 ml/gm; $n = 0.51$). The free fraction of the nonspecific distribution volume (f_2) was not different between groups (controls, 0.43 ± 0.18%; patients, 0.47 ± 0.21%; $p = 0.55$).

ROI volumes

Table 2 lists the ROI volumes in healthy controls and patients with schizophrenia. No significant between-group differences were found in DLPFC volumes, nor in volumes of the other regions. A trend was observed for the hippocampus ($p = 0.05$) and parahippocampal gyrus ($p = 0.07$) volumes to be smaller in patients with schizophrenia compared with controls, by 13 and 9%, respectively.

[^{11}C]NNC 112 delivery to the brain

No significant between-group differences were observed in the regional rates of tracer delivery to the brain, as measured by the parameter K_1. For example, DLPFC K_1 was 0.14 ± 0.03 $ml \cdot gm^{-1} \cdot min^{-1}$ in control subjects and 0.15 ± 0.04 $ml \cdot gm^{-1} \cdot min^{-1}$ in patients with schizophrenia ($p = 0.46$). Assuming that patients and controls have similar permeability–surface

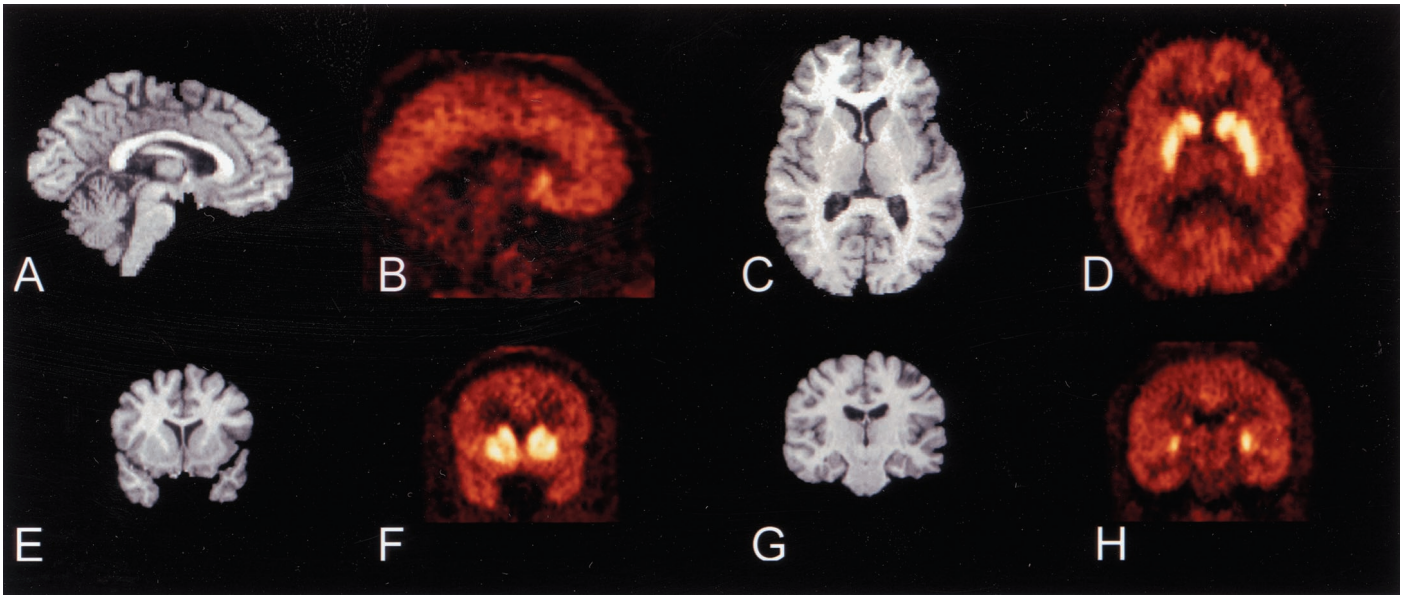

Figure 3. MRI and coregistered [^{11}C]NNC 112 PET images. The PET image represents the activity recorded from 30 to 60 min after injection of 13.3 mCi in a 37-year-old healthy female volunteer. *A*, *B,* Sagittal view, illustrating the contrast between cortical and cerebellar activities. *C, D,* Transaxial view, at the level of the head of caudate, putamen, and thalamus. *E*, *F,* Coronal view, at the level of the anterior striatum, illustrating the lower level of activity in the ventral striatum compared with the caudate and putamen. *G*, *H,* Coronal view at the level of the hippocampus, illustrating low levels of activity in thalamus, hippocampus, and parahippocampal gyrus. Putamen and caudate activities are still visualized.

area product for [^{11}C]NNC 112, this result indicates no significant between-group difference in regional blood flow.

[^{11}C]NNC 112 regional BP

The regional uptake of [^{11}C]NNC 112 was consistent with the known distribution of D_1 receptors in the human brain. Representative images and regional time–activity curves are presented in Figures 3 and 4, respectively.

DLPFC [^{11}C]NNC 112 BP was significantly higher in patients with schizophrenia compared with control subjects ($p = 0.02$) (Table 3). The distribution of DLPFC [^{11}C]NNC 112 BP values in each group is presented in Figure 5. The variance was not different between groups (F test; $p = 0.70$). One value in the patients group was an outlier, with z score of 2.26. No rationale was identified to exclude this observation *a posteriori*. Nonetheless, the analysis was repeated without this value, and provided similar results ($p = 0.038$). The absence of significant between-group differences in DLPFC volume indicates that the between-group difference in DLPFC [^{11}C]NNC 112 BP was not attributable to partial voluming effects.

Table 3 also lists [^{11}C]NNC 112 BP values in other regions. A trend was observed for higher [^{11}C]NNC 112 BP in the MPFC ($p = 0.08$) and temporal cortex ($p = 0.08$; values not corrected for multiple testing). Other regions did not show significant between-group differences in [^{11}C]NNC 112 BP. Principal component analysis was applied to [^{11}C]NNC 112 BP values from the 14 regions included in Table 3. This analysis returned three significant factors (eigenvalues higher than 1) that accounted for 87% of the variance. The regional weights associated with each factor are presented in Table 4. Factor 1 accounted for 54% of the variance, showed high loads for anterior neocortical regions, and was termed frontocortical factor. Factor 2 accounted for 19% of the variance and was essentially contributed to by the striatal regions. A third factor was extracted, accounting for 10% of the variance and showing high loads in hippocampus and thalamus

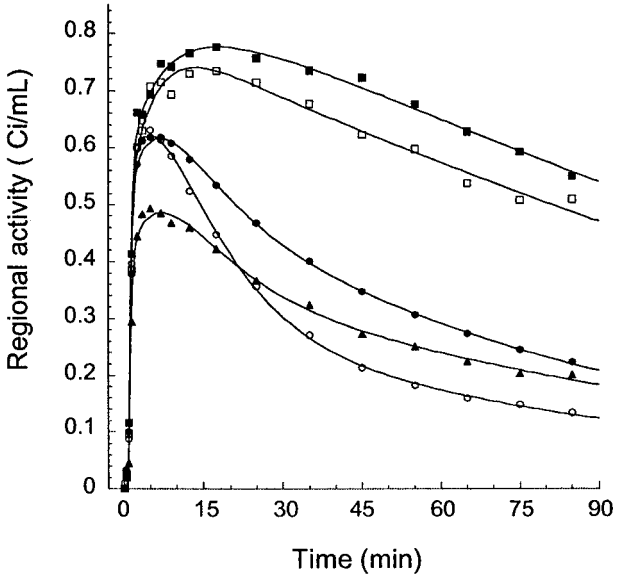

Figure 4. Regional time-activity curves after injection of 16.6 mCi [^{11}C]NNC 112 in a 42-year-old male healthy volunteer. Only a subset of regions are represented: dorsal caudate (*closed squares*), ventral striatum (*open squares*), dorsolateral prefrontal cortex (*closed circles*), hippocampus (*closed triangles*), and cerebellum (*open circles*). *Points* are measured values for each frame, and *lines* are values fitted to a three compartment model.

only. Individual values on each factor were computed by multiplying the z score matrix of regional [^{11}C]NNC 112 BP value by the factor weight matrix. Repeated measure ANOVA with factors as repeated measure and diagnosis as factor showed no diagnosis effect ($p = 0.62$), but a significant factor by diagnosis interaction ($p = 0.036$). *Post hoc* analysis revealed that patients with schizophrenia had significantly higher values on factor 1 compared with controls ($p = 0.016$). No significant differences were observed in

Table 3. [^{11}C]NNC 112 binding potential in controls and patients with schizophrenia (ml/gm)

Region	Subregion	Controls	Patients
Neocortex	DLPFC	1.27 ± 0.44	1.63 ± 0.39*
	MPFC	1.57 ± 0.33	1.82 ± 0.44
	OFC	1.41 ± 0.44	1.69 ± 0.72
	TC	1.55 ± 0.34	1.82 ± 0.49
	PC	1.46 ± 0.41	1.63 ± 0.44
	OC	1.51 ± 0.42	1.70 ± 0.38
Limbic/paralimbic	ACC	1.74 ± 0.50	1.93 ± 0.37
	AMY	1.42 ± 0.39	1.51 ± 0.48
	HIP	1.31 ± 0.86	1.18 ± 0.39
	PHG	1.14 ± 0.40	1.31 ± 0.43
Striatum	DCA	5.93 ± 2.68	6.36 ± 1.35
	DPU	6.72 ± 2.44	6.90 ± 1.49
	VST	5.71 ± 2.73	5.48 ± 1.57
Thalamus		0.98 ± 0.43	0.91 ± 0.28

Values are mean ± SD; $n = 16$ per group. DLPFC, Dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; ACC, anterior cingulate cortex; AMY, amygdala; HIP, hippocampus; PHG, parahippocampal gyrus; DCA, dorsal caudate; DPU, dorsal putamen; VST, ventral striatum.

*$p<0.05$.

factors 2 ($p = 0.38$) and 3 ($p = 0.21$). Together, these data indicated a relatively diffuse and significant increase in neocortical D_1 receptor availability in patients with schizophrenia, most pronounced in DLPFC.

[^{11}C]NNC 112 regional V_3''

Results obtained with V_3'' (=BP/V_2) were essentially similar to results obtained with BP, which was expected from the absence of between-group differences in V_2. Thus, DLPFC was the only region showing a significant difference in [^{11}C]NNC 112 V_3'' (higher in patients compared with controls; $p = 0.03$).

DLPFC D_1 receptors BP and clinical variables

A significant age-related decline in DLPFC [^{11}C]NNC 112 BP was observed in the entire sample ($r^2 = 0.13$; $p = 0.02$) (Fig. 6). This relationship was present in both groups, but failed to reach significance when groups were analyzed separately (control subjects: $r^2 = 0.11$, $p = 0.08$; patients with schizophrenia, $r^2 = 0.17$, $p = 0.11$). No age by diagnosis interaction was observed for DLPFC [^{11}C]NNC 112 BP ($p = 0.62$), suggesting that age affected both groups similarly.

In the patient group, DLPFC [^{11}C]NNC 112 BP was not significantly different between first episode–antipsychotic drug-naive patients ($n = 7$; age = 30 ± 13 years; DLPFC [^{11}C]NNC 112 BP = 1.64 ± 0.23 ml/gm) and chronic patients previously exposed to antipsychotic medications ($n = 9$; age = 35 ± 12 years; DLPFC [^{11}C]NNC 112 BP = 1.62 ± 0.50 ml/gm; $p = 0.94$). Among the previously treated patients, five underwent inpatient washout and had a relatively brief drug-free interval before the PET scan (19 ± 3 d), and four were not taking antipsychotic drugs for at least 1 year before the PET scan. DLPFC [^{11}C]NNC 112 BP was not different between previously treated patients with short (1.70 ± 0.55 ml/gm) or long drug-free interval (1.52 ± 0.40 ml/gm; $p = 0.62$). In previously treated patients, no relationship was observed between duration of the drug-free interval and DLPFC [^{11}C]NNC 112 BP ($r^2 = 0.03$; $p = 0.66$). Together, these data indicate that the upregulation of D_1 receptors in the DLPFC in patients with schizophrenia was not related to previous exposure to antipsychotic medications.

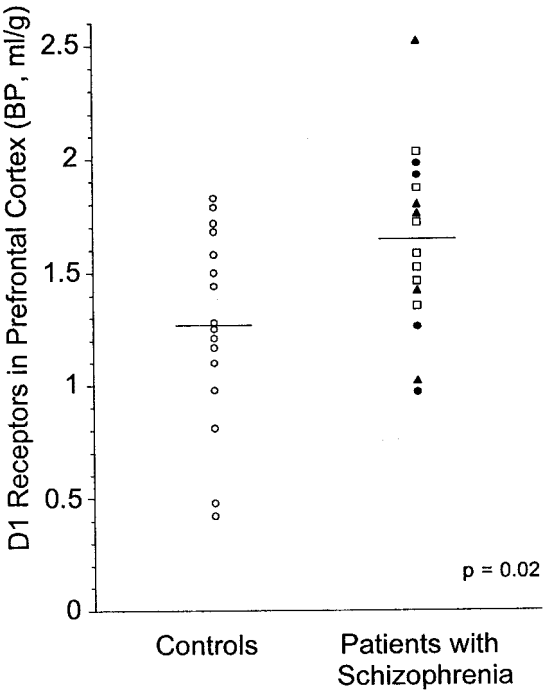

Figure 5. Distribution of [^{11}C]NNC 112 BP in DLPFC of healthy controls ($n = 16$; open circles) and patients with schizophrenia ($n = 16$; antipsychotic-naive patients, *open squares;* patients antipsychotic-free for >1 year, *closed circles;* patients with 2–3 weeks of antipsychotic-free interval, *closed triangles*). Patients with schizophrenia displayed increased D_1 receptor availability compared with controls ($p = 0.02$).

In the patient group, DLPFC [^{11}C]NNC 112 BP was not significantly associated with severity of positive symptoms as assessed by the PANSS-positive subscale ($r^2 = 0.02$; $p = 0.65$), nor with severity of negative symptoms (PANSS-negative subscale; $r^2 = 0.04$; $p = 0.21$), nor with general psychopathology (PANSS general psychopathology scale; $r^2 = 0.04$; $p = 0.46$). DLPFC [^{11}C]NNC 112 BP was not associated with duration of illness ($r^2 = 0.03$; $p = 0.49$).

DLPFC D_1 receptors BP and working memory performance

The hypothesis of an association between D_1 receptor availability in DLPFC and n-back performance was tested in the entire sample and in each group separately (Table 5). When analyzing both groups together, an association was observed between low working memory performance at 1-, 2-, and 3-back and high DLPFC [^{11}C]NNC 112 BP. This effect was accounted for by the patients with schizophrenia. Within the control group, there was no relationship between performance on the n-back and D_1 receptor availability. In patients with schizophrenia, high DLPFC D_1 receptor availability was associated with low AHR at 2-back ($r^2 = 0.31$; $p = 0.04$) and at 3-back ($r^2 = 0.45$; $p = 0.008$). Similar results were observed with d′ (2-back, $r^2 = 0.29$, $p = 0.04$; 3-back, $r^2 = 0.43$, $p = 0.01$). The relationship between DLPFC [^{11}C]NNC 112 BP and AHR at the 3-back condition is presented in Figure 7.

DISCUSSION

The main findings of this study are that DLPFC D_1 receptor availability, measured by the *in vivo* binding of [^{11}C]NNC 112, is

Table 4. [^{11}C]NNC 112 binding potential: principal component analysis

Region	Subregion	Factor 1 (frontocortical)	Factor 2 (striatal)	Factor 3 (thalamolimbic)
Neocortex	DLPFC	0.83	0.00	−0.40
	MPFC	0.73	0.07	−0.09
	OFC	0.67	−0.05	−0.22
	TC	0.65	0.07	0.11
	PC	0.59	0.00	0.21
	OC	0.49	0.04	0.35
Limbic/paralimbic	ACC	0.43	0.06	0.32
	AMY	0.31	0.04	0.42
	HIP	−0.19	−0.13	0.82
	PHG	0.44	−0.11	0.40
Striatum	DCA	0.07	0.81	−0.18
	DPU	0.00	0.81	0.13
	VST	−0.19	0.89	−0.04
Thalamus		−0.16	0.01	0.89

Values are regional weights for the three factors derived from principal component analysis of the entire sample (n = 32). DLPFC, Dorsolateral prefrontal cortex; MPFC, medial prefrontal cortex; OFC, orbitofrontal cortex; TC, temporal cortex; PC, parietal cortex; OC, occipital cortex; ACC, anterior cingulate cortex; AMY, amygdala; HIP, hippocampus; PHG, parahippocampal gyrus; DCA, dorsal caudate; DPU, dorsal putamen; VST, ventral striatum.

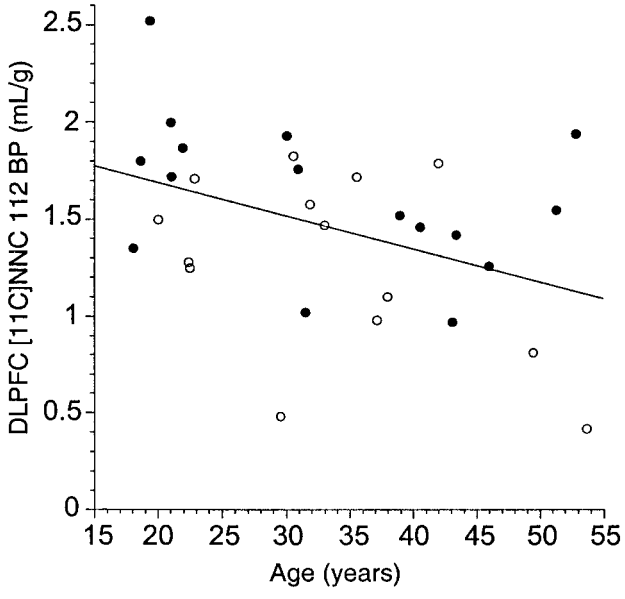

Figure 6. Effect of aging on [^{11}C]NNC 112 BP in DLPFC of healthy controls (*open circles*) and patients with schizophrenia (*closed circles*). A significant age-related decline in DLPFC [^{11}C]NNC 112 BP was observed in the entire sample ($r^2 = 0.13$; $p = 0.02$). No age by diagnosis interaction was observed for DLPFC [^{11}C]NNC 112 BP ($p = 0.62$), suggesting that age affected both groups similarly.

increased in never-treated and currently untreated patients with schizophrenia, and that this increase is a strong predictor of decreased performance at the n-back task.

Because of the evidence implicating DLPFC DA transmission in working memory processes, evaluation of [^{11}C]NNC 112 BP in the DLPFC was the primary focus of this study. Other regions were also investigated to assess the regional specificity of the results in the DLPFC. The DLPFC was the only region examined in which a significant difference in [^{11}C]NNC 112 BP was found between patients with schizophrenia and controls. However, principal component analysis indicated that the alteration of DA transmission associated with increased [^{11}C]NNC 112 BP might not be restricted to the DLPFC, because other cortical regions such as MPFC showed high covariance with DLPFC. Analysis of a larger sample is required to further explore this issue. In contrast, there was no indication for alterations in [^{11}C]NNC 112 BP in striatal, limbic, and thalamic regions.

The absence of change in striatal [^{11}C]NNC 112 BP observed in this study is consistent with postmortem studies that reported unaltered striatal binding of [^{3}H]SCH 23390 in schizophrenia (Pimoule et al., 1985; Seeman et al., 1987; Joyce et al., 1988; Reynolds and Czudek, 1988), although one study reported decreased striatal binding of [^{3}H]SCH 23390 in schizophrenia (Hess et al., 1987).

The significant increase in DLPFC [^{11}C]NNC 112 BP observed in patients with schizophrenia contrasts with results of three previous postmortem studies. Two studies evaluated the binding of [^{3}H]SCH 23390 in the PFC in schizophrenia. One homogenate binding study reported no change (Laruelle et al., 1990), and one autoradiography study reported a nonsignificant increase (Knable et al., 1996). PFC D_1 receptor mRNA levels were also reported unchanged (Meador-Woodruff et al., 1997). These postmortem results might be affected by antemortem medications, because administration of antipsychotic drugs downregulate PFC D_1 receptor mRNA and proteins (Lidow and Goldman-Rakic, 1994; Lidow et al., 1997).

The results presented here contrast with the results of a previous PET study that reported lower [^{11}C]SCH 23390 k_3/k_4 ratio (V_3'' in our notation) in the PFC in patients with schizophrenia (Okubo et al., 1997). In addition to potential clinical differences in clinical populations and symptoms severity, several critical technical factors limit the comparability of these studies: (1) the PFC–cerebellum distribution volume ratio of [^{11}C]SCH 23390 is in the 1.2–1.4 range, versus 1.7–2 for [^{11}C]NNC 112, indicating that [^{11}C]NNC 112 is a superior ligand for the measurement of D_1 receptors in the PFC; (2) the PET camera used by Okubo et al. (1997) was a seven slices device, with limited field of view and limited resolution compared with the camera used in this study; (3) [^{11}C]SCH 23390 displays a relatively low selectivity against $5HT_{2A/2C}$ receptors (Laruelle et al., 1991), whereas [^{11}C]NNC 112 *in vivo* binding in the PFC is not affected by pretreatment

Table 5. Association between DLPFC [^{11}C]NNC 112 BP and performance at n-back (Adjusted Hit Rate)

	All subjects (n = 28)		Control subjects		Patients with schizophrenia		
Task level	r	p	r	p	r	p	Interaction p
1-back	−0.44	0.02	0.04	0.88	−0.43	0.12	0.044
2-back	−0.42	0.02	0.23	0.07	−0.55	0.04	0.008
3-back	−0.62	0.01	−0.05	0.41	−0.67	0.008	0.094

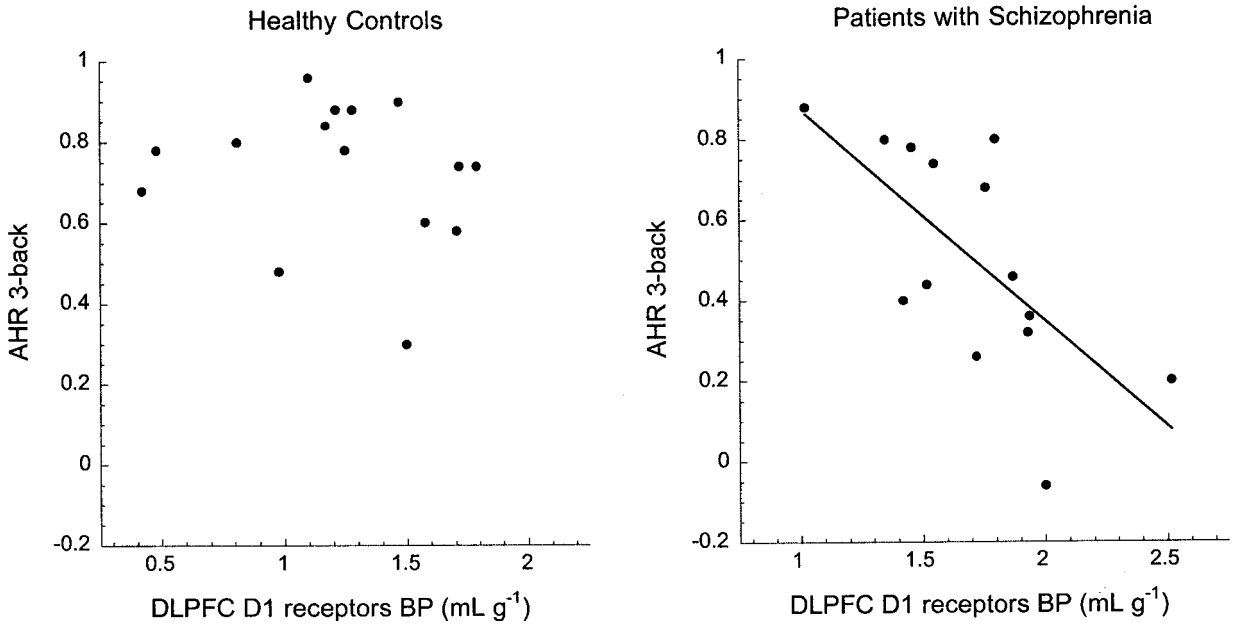

Figure 7. Relationship between [^{11}C]NNC 112 BP in DLPFC (x-axis) and performance (*AHR*) at the 3-back test (y-axis) in healthy controls (*left*) and in patients with schizophrenia (*right*). The AHR ranges from 1 (best performance) to −1 (worse performance), with a score of 0 corresponding to performance at chance level. In controls, DLPFC D_1 receptor availability was not associated with performance at the task. In patients with schizophrenia, increased DLPFC D_1 receptor availability was associated with low performance at the task (r^2 = 0.45; p = 0.008). Note the difference in x-axis scales between controls and patients with schizophrenia. Similar findings were observed with the 2-back (Table 5).

with selective $5HT_{2A/2C}$ antagonists (Halldin et al., 1998); (4) several lines of evidence suggest that the cellular localization of D_1 receptors differentially influence the *in vivo* binding of [^{11}C]SCH 23390 and [^{11}C]NNC 112 (for review, see Laruelle, 2000). Acute DA depletion has no effect on the *in vivo* binding of [^{11}C]NNC 112, but decreases the *in vivo* binding of [^{3}H]SCH 23390 (Guo et al., 2000), an effect that might be attributable to receptor translocation from the endosomial compartment to the cell surface and lower *in vivo* affinity of SCH 23390 for externalized compared with internalized receptors (Dumartin et al., 2000; Laruelle, 2000). In addition, sustained DA depletion induced by chronic reserpine treatment (21 d) is associated with increased *in vivo* [^{11}C]NNC 112 binding in the rat PFC (presumably reflecting increase in D_1 receptor expression) (Guo et al., 2001). However, the same treatment failed to produce detectable changes in the *in vivo* binding of [^{3}H]SCH 23390 in the PFC (Guo et al., 2001), maybe because the opposite effects of receptor upregulation and externalization on [^{3}H]SCH 23390 *in vivo* binding cancel each other. Further research is warranted to elucidate the role of these factors in the discrepant findings between these two studies.

Patients enrolled in this study performed significantly worse than controls at each working memory load, but, even at the challenging 3-back load, performed significantly above chance level. This observation might reflect a selection bias toward patients with moderate pathology, because of the rigor of the capacity to consent evaluation. In these patients, increased DLPFC D_1 receptor availability was a strong predictor of poor performance at the 2-back and 3-back conditions (approximately one-third of the variance in 2- and 3-back AHR was accounted for by the variance in DLPFC [^{11}C]NNC 112 BP). This relationship supports the involvement of altered DLPFC D_1 receptor transmission in the working memory deficits presented by these patients. Although it has been argued that working memory deficit might be the fundamental cognitive impairment in schizophrenia (Goldman-Rakic, 1994), patients with schizophrenia are impaired on multiple cognitive dimensions such as attention, learning and memory, executive function, and general intelligence (Braff et al., 1991; Saykin et al., 1994). Studies in a larger sample of subjects characterized with a comprehensive neuropsychological battery are warranted to test the specificity of the association between increased D_1 receptor availability and working memory deficits.

The *in vivo* binding of [^{11}C]NNC 112 is not affected by acute changes in endogenous DA (Abi-Dargham et al., 1999; Chou et al., 1999; Guo et al., 2000). It is therefore reasonable to assume that the increased [^{11}C]NNC 112 binding observed in this study reflects increased concentration of D_1 receptors in DLPFC of patients with schizophrenia. This increased concentration might

represent a primary phenomenon or a compensatory upregulation secondary to chronic deficiency in D_1 receptor stimulation by DA. At this point, both possibilities must be entertained, but the second hypothesis is favored by several lines of evidence.

The first interpretation (increase in DLPFC D_1 receptor is a primary phenomenon) might suggest that the alteration in working memory performance seen in these patients results from increased postsynaptic sensitivity to DA released in the DLPFC during performance of the task (Watanabe et al., 1997). This view is consistent with the evidence that excessive stimulation of D_1 receptors, either because of excessive DA release or to high doses of DA agonists (Arnsten et al., 1994; Murphy et al., 1996a,b; Cai and Arnsten, 1997; Zahrt et al., 1997), is associated with a deterioration of working memory function in primates. This interpretation would predict that administration of D_1 antagonists should improve working memory function in patients with schizophrenia. While we are not aware of studies that specifically evaluated the effect of D_1 receptor antagonists on working memory function in schizophrenia, limited therapeutic trials with selective D_1 receptor antagonists in schizophrenia showed a lack of efficacy or even worsening of clinical conditions (de Beaurepaire et al., 1995; Den Boer et al., 1995; Karle et al., 1995; Karlsson et al., 1995).

The second interpretation (increase in DLPFC D_1 receptors is a compensatory response to deficit in presynaptic DA function) is consistent with several indirect lines of evidence suggesting that schizophrenia might be associated with a deficit in prefrontal DA function. This hypothesis was proposed based on the relationship between low CSF homovanillic acid and poor performance at tasks involving the DLPFC in schizophrenia (Weinberger et al., 1988; Kahn et al., 1994), and on the beneficial effect of DA agonists on the pattern of DLPFC activation measured with PET during these tasks (Daniel et al., 1989, 1991; Dolan et al., 1995). More direct evidence for such a deficit was recently provided by one postmortem study suggesting a decrease in DA innervation in the DLPFC (Akil et al., 1999). This interpretation is also consistent with the performance deficits at delayed-response tasks observed in nonhuman primate models of prefrontal DA deficiency (selective 6-OHDA-induced DA depletion in the PFC, aged monkeys, and monkeys chronically treated with haloperidol). These deficits are reversed by indirect DA agonists and D_1 agonists (Brozoski et al., 1979; Arnsten et al., 1994; Cai and Arnsten, 1997; Castner et al., 2000). This view is also supported by the observation that chronic phencyclidine exposure, which induces in humans symptoms reminiscent of schizophrenia (for review, see Javitt and Zukin, 1991), is associated with both impaired working memory performance and decreased DA turnover in the PFC in rodents and primates (for review, see Jentsch and Roth, 1999).

The observation that chronic DA depletion is associated with increased *in vivo* binding of [^{11}C]NNC 112 in the PFC supports the plausibility of this interpretation of the PET findings (Guo et al., 2001). If this hypothesis is correct, both the increase in DLPFC [^{11}C]NNC 112 BP and the decrease in n-back performance would be related to a common cause, i.e., a deficit in mesocortical presynaptic DA function. The similarity in DLPFC [^{11}C]NNC 112 BP between first episode and chronic patients and the absence of association between this parameter and duration of illness are consistent with the hypothesis that this mesocortical DA function deficiency might be of neurodevelopmental origin (Weinberger, 1987). This interpretation suggests that working memory function in patients with schizophrenia might be improved by DA agonists.

A third possible interpretation of the data that combines elements of the first and second interpretations should also be discussed. A persistent decrease in prefrontal DA activity might induce upregulation of D_1 receptors. This upregulation, which could be associated with increased sensitivity to agonists, might create conditions in which the increase in DA associated with stress or cognitive demands would result in an overstimulation of these upregulated D_1 receptors. This model would predict that acute administration of a D_1 receptor agonist might be detrimental, although repeated administration of a D_1 agonist might lead to desensitization of the receptors and thus have long term therapeutic effects. The development of an effective D_1 receptor agonist suitable for human administration is critical to test these predictions.

Conclusions

In this study, D_1 receptor availability was measured *in vivo* with PET and [^{11}C]NNC 112 in untreated patients with schizophrenia and controls. [^{11}C]NNC 112 BP was significantly elevated in the DLPFC, as well as, to a lower extent, in other anterior cortical regions. This increase was not caused by previous antipsychotic medications and was not associated with the severity of clinical symptomatology. However, excessive expression of D_1 receptor in the DLPFC was strongly associated with impaired performance at the n-back task, a test of working memory function, confirming in humans the critical role of prefrontal D_1 receptor transmission in delayed-response tasks observed in animal studies. We propose that both D_1 receptor upregulation and impaired working memory performance might be caused by a chronic deficit in presynaptic DA function in the DLPFC of patients with schizophrenia. Additional imaging studies are warranted to confirm these data in an extended sample, to study the specificity of the relationship between cortical D_1 receptor expression and working memory relative to other cognitive impairments, and to evaluate the relationship between prefrontal presynaptic DA function and D_1 receptor availability in patients with schizophrenia.

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