D1-Dopamine Receptor Availability in First-Episode Neuroleptic Naive Psychosis Patients

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Abstract

Background: Positron emission tomography studies examining differences in D1-dopamine receptor binding between control subjects and patients with schizophrenia have been inconsistent, reporting higher, lower, and no difference in the frontal cortex. Exposure to antipsychotic medication has been suggested to be a likely source of this heterogeneity, and thus there is a need for studies of patients at early stages of the disorder who have not been exposed to such drugs.

Methods: Here, we compared 17 healthy control subjects and 18 first-episode neuroleptic naive patients with schizophrenia or schizophreniform psychosis using positron emission tomography and the D1-dopamine receptor radioligand [11C]SCH23390.

Results: We observed a statistically significant difference in the dorsolateral prefrontal cortex. Contrary to our expectations, patients had less D1-dopamine receptor availability with a moderate effect size. In a Bayesian analysis, we show that the data are over 50 times more likely to have occurred under the decrease as opposed to the increase hypothesis. This effect was not global, as our analysis showed that the null hypothesis was preferred over either hypothesis in the striatum.

Conclusions: This investigation represents the largest single sample of neuroleptic-naive patients examined for D1-dopamine receptor availability using PET and suggests a reduction of prefrontal D1-dopamine receptor density in the pathophysiology of schizophrenia. However, further work will be required to reach a consensus.

Key words: schizophrenia, drug naïve, positron emission tomography, D, dopamine receptor, dorsolateral prefrontal cortex

Introduction

The dopamine system has been of central interest in the pathophysiology of schizophrenia for more than 50 years. Indeed, molecular imaging studies using positron emission tomography (PET) have provided a great deal of evidence for elevations in both presynaptic dopamine synthesis capacity and amphetamine-induced dopamine release in schizophrenia patients compared with controls (Howes and Kapur, 2009). Regarding dopamine receptor subtypes, the striatal D2-dopamine receptor (D2R) availability has been examined in numerous studies, providing some evidence for a small increase in patients compared with controls (Howes et al., 2012). In contrast, only a few PET studies have examined the D1-dopamine receptor (D1R) in schizophrenia. Compared with the D2R, there is a much higher concentration of D1R in the cortex (Hall et al., 1994), and the frontal cortex in particular is thought to be a crucial brain region.
for understanding the biological basis for schizophrenia (Selemon and Goldman-Rakic, 1999; Callicott et al., 2000; Wagstyl et al., 2016).

However, in vivo studies of the D1R in patients with schizophrenia have yielded mixed results (Cervenka, 2019). Initial studies using the radioligands [11C]SCH23390 or [11C]NNC112 found lower (Okubo et al., 1997), higher (Abi-Dargham et al., 2002), or no difference (Karlsson et al., 2002) in the availability of D1R in the frontal cortex compared with healthy control subjects. The former 2 research groups have both replicated their own respective results in chronic medicated patients (Kosaka et al., 2010) and in a subsample of drug-naive patients (Abi-Dargham et al., 2012), respectively. In another small sample of twin pairs discordant for schizophrenia, Hirvonen et al. (Hirvonen et al., 2006) reported lower D1R binding in chronic, medicated schizophrenia probands compared with controls. In contrast, higher levels were shown in monzygotic unaffected co-twins, that is, individuals at high genetic risk.

Importantly, in studies where both neuroleptic naive and either medicated or drug-free patients were examined, the latter group has consistently exhibited numerically lower D1R binding compared with the former (Okubo et al., 1997; Abi-Dargham et al., 2002, 2012; Poels et al., 2013; Cervenka, 2019). This may be explained by a reduction in D1R due to antipsychotic treatment as has been shown in experimental studies of nonhuman primates (NHPs) (Lidow and Goldman-Rakic, 1994; Lidow et al., 1997) although not confirmed in a human postmortem study Knable et al. (Knable et al., 1996). Moreover, in the case of ongoing medication (Hirvonen et al., 2006; Kosaka et al., 2010), caution must be exercised since a direct D1R occupancy has been shown for some antipsychotic drugs (Farde et al., 1992). To avoid this confounding factor, researchers need to understand the role of the D1R in schizophrenia needs to focus on the early stages of the illness, that is, before antipsychotic treatment.

Though the PET studies of the D1R in schizophrenia patients have been conducted with small sample sizes, and therefore with low statistical power, a tentative interpretation of the results is that drug-naive patients with psychosis disorders, and potentially also unmedicated individuals at high genetic risk for schizophrenia, show higher D1R binding in frontal cortex (Cervenka, 2019).

To test this hypothesis, we used PET and the radioligand [11C]SCH23390 to examine 18 neuroleptic-naive, first-episode psychosis patients and 18 healthy controls and compared the availability of the D1R between the groups in the dorsolateral prefrontal cortex and striatum.
Table 1. Demographic Characteristics and BPRS Scores for 18 Patients With Schizophrenia or Schizoaffective Disorder

| Patient no | Age (y) | Sex | BPRS total score | BPRS positive symptoms score | BPRS negative symptoms score | Diagnosis at 1-year follow-up |
|------------|---------|-----|------------------|-------------------------------|-----------------------------|-----------------------------|
| 1          | 28      | F   | 48               | 18                           | 9                           | Schizophrenia               |
| 2          | 21      | M   | 46               | 15                           | 15                          | Schizophrenia               |
| 3          | 35      | F   | 52               | 17                           | 7                           | Schizoaffective disorder    |
| 4          | 19      | F   | 37               | 15                           | 10                          | Schizophrenia               |
| 5          | 22      | M   | 26               | 11                           | 4                           | Schizophrenia               |
| 6          | 32      | M   | 50               | 19                           | 12                          | Schizophrenia               |
| 7          | 22      | M   | 41               | 15                           | 11                          | Schizophrenia               |
| 8          | 39      | M   | 60               | 24                           | 9                           | Schizophrenia               |
| 9          | 35      | M   | 59               | 24                           | 9                           | Schizophrenia               |
| 10         | 33      | F   | 36               | 14                           | 9                           | Schizophrenia               |
| 11         | 32      | M   | 33               | 16                           | 3                           | Schizophrenia               |
| 12         | 41      | M   | 27               | 11                           | 5                           | Schizophrenia               |
| 13         | 41      | M   | 31               | 14                           | 5                           | Schizophrenia               |
| 14         | 36      | F   | 33               | 18                           | 3                           | Schizophrenia               |
| 15         | 21      | M   | 41               | 16                           | 10                          | Schizophrenia               |
| 16         | 49      | M   | 41               | 14                           | 13                          | Schizophrenia               |
| 17         | 51      | F   | 58               | 24                           | 15                          | Schizophrenia               |
| 18         | 22      | F   | 35               | 7                            | 3                           | Schizophrenia               |

General Comments on MRI and PET Imaging

Due to the 14 years between examination of the first and the last subject, there were technical changes along the way in some of the experimental procedures. The changes comprised the use of different MRI protocols, the use of Neuroinsert (a PET gantry device in lead shielding radiation originating from the trunk), the PET acquisition time length, reconstruction parameters, and file formats. The experimental procedures and settings are for each individual listed in Supplementary Materials 2. As described below, the differences in experimental procedures were, when so required, included as confounders in the statistical analysis.

MRI Examination

All subjects underwent a T2-weighted MRI measurement to rule out any brain abnormality. In the beginning of data collection, only the T2 sequence was performed (n=16) on a 1.5-T Signa unit (General Electric, Milwaukee, WI). A standard spin-echo sequence with a 256 × 256 matrix was used with a repetition time of 4 seconds. Echo times 85 msec with a total scanning time of about 10 minutes. The long echo time was to enhance the grey and white matter segmentation to allow the delineation of regions of interest (ROIs). The rationale for having only one MRI sequence was to reduce the risk of noncompliance with a longer examination including several sequences. In addition, the primary purpose of the MRI was a clinical examination to rule out any pathology.

Later in the data collection, software and coil upgrade with improved MR sequences allowed for shorter scanning time, and the remaining subjects (n=19) had, in addition to the T2-weighted protocol, a T1-weighted sequence for improved grey and white matter segmentation with a total scanning time of about 10 minutes. This T2 protocol was based on the following sequence: repetition time/echo time = 6060/92.6 milliseconds, field of view 260 mm, image matrix 256 × 256, thickness/spacing 3/0.1 mm, flip angle 150°, slice thickness = 5 mm. The T1 protocol was based on a 3-dimensional axial Spoiled Gradient Recalled Acquisition with the following sequence: repetition time/echo time = 20/5 milliseconds, field of view 260 mm, image matrix 256 × 256, thickness/spacing 1/0 mm, flip angle 35°.

PET Examination

For each subject, PET examinations were performed on the Siemens ECAT EXACT HR PET system. Radioactivity in brain was measured with 2D data acquisition, except for 2 subjects who had 3D data acquisition. The spatial resolution in the reconstructed sections is 3.8 mm at the center of the field of view (Wienhard et al., 1994). A transmission scan was performed using 3 rotating 68Ge rod sources for about 5 minutes.

To minimize head movement during the PET measurement, a plaster helmet was made for each subject individually and used during the PET measurement (Bergstrom et al., 1981). At the start of the PET measurement, a sterile phosphate buffer (pH = 7.4) containing [11C]SCH23390 was injected as a bolus during several seconds into the cubital vein. The venous catheter was then immediately flushed with up to 10-ml saline solution.

[11C]SCH23390 was prepared as previously described (Halldin et al., 1986). The injected radioactivity was 317 ± 22 MBq (mean, SD). The molar activity was not analyzed for 2 of the healthy controls and 1 of the patients due to the small amount of product left in the vial after injection. The molar radioactivity for the remaining 32 subjects was 104 ± 133 MBq/nmol, which corresponded to an injected mass of 3.6 ± 5.7 μg (range 0.17–32 μg, median 2.62 μg). All subjects received 8 μg or less except for one patient who received 32 μg. This was due to delay of injection with subsequent decrease in molar radioactivity. Estimation of D1R occupancy by 32 μg SCH23390 based on published data is 6.0%, that is, the binding potential (BPND) was underestimated by 6%, which was corrected for in the statistical analysis by dividing this subject’s subjects BPND value by 0.94 (Farde, 1992; Fischer et al., 2010). The radioactivity and mass did not differ significantly between the patients and controls.

The PET protocol for each individual is listed in Supplementary Materials 2. Following injection, emission data were collected in a sequence of time frames. The time frames of acquisition data were reconstructed and corrected for attenuation and scatter using 2D filtered-back projection into a series of 3D PET images of radioactivity concentration. The voxel size for the reconstructed volume was 2.030 × 2.030 × 3.125 mm.
Image Processing and Quantification

Despite the collection of data being conducted over several years, all image processing and quantification of the data were performed at the same time during 2018 using current analysis software. Three-dimensional PET images were for each time frame corrected for head motion using a postreconstruction frame-by-frame realignment algorithm, in which the dynamic PET image was first divided into blocks of frames of a minute or longer, that is, frames of less than a minute were summed together. Then all images were individually aligned to the first minute of acquisition using the SPM5 (Wellcome Department of Cognitive Neurology, University College London) (Friston et al., 1995). Integral PET images were created using ecatsum (v 1.4.3, Turku PET Centre). Finally, MR images were reoriented into the AC-PC plane and coregistered to integral PET images using SPM5.

Kinetic modelling was performed using the R package kinftr (v 0.2.0) (https://github.com/mathesong/kinfitr). Regional BPND per cent values were calculated using the simplified reference tissue model with the cerebellar grey matter as reference region (Lammertsma and Hume, 1996).

ROI Delineation

The MR images were used to delineate anatomical ROIs for the striatum (STR) (caudate and putamen), the dorsolateral prefrontal cortex (DLPFC) and the cerebellum (CBL). The STR and DLPFC were chosen since they are regions of central interest in schizophrenia research. For the DLPFC, several convergent findings relevant for schizophrenia and D1R transmission have been reported (Arnsen et al., 2017). In addition, we performed an exploratory analysis of additional cortical regions—anterior cingulate cortex (ACC), temporal cortex (TC), medial prefrontal cortex (MPFC), and orbito frontal cortex (OFC)—based on previous studies investigating D1-R in psychosis (Okubo et al., 1997; Abi-Dargham et al., 2002, 2012; Kosaka et al., 2010). The CBL was chosen as reference region for the concentration of free and nonnegligible fraction of cortical binding, and differences in this fraction might cause systematic differences (Ekelund et al., 2007). Although this fraction has been shown to be similar for both radioligands 5-HT2A receptor binding contributes to a nonnegligible fraction of cortical binding, and differences in this fraction might cause systematic differences (Ekelund et al., 2007). Although this fraction has been shown to be similar in magnitude for both tracers, for [11C]NNC112 this estimate was derived from a PET examination of only 2 baboons and not from humans (Ekelund et al., 2007). Lastly, in studies using [11C]NNC112, the main outcome parameter has been BPND, calculated in all cases but one (Kosaka et al., 2010) using arterial plasma measurements (Abi-Dargham et al., 2002; Abi-Dargham et al., 2012). To assure that these hypotheses were not differentially influenced by different sizes of previously reported effects, we opted to use the same scale for both the increase and decrease prior based on a weighted average of previous differences. We therefore used a SD of 31% for DLPFC and of 21% for the STR. More details regarding selection of priors are provided in Supplementary Materials 1.

We also tested whether other factors differing between measurements might have a substantial impact on the results and thereby act as a confounder. These factors relate to PET acquisition (2D or 3D PET acquisition, presence of absence of the Neuroimsert, measurement length, date of measurement, i.e.,
To reject the null hypothesis based on a nonsignificant statistically invalid approach of accepting (as opposed to failing desirable to assess equivalence within more restrictive equivalence bounds within which the outcomes are assumed to be sufficiently similar. We performed a power analysis for the equivalence bound for 2-sample equivalence tests with a type I error rate of 0.05, a power of 0.8, and samples of 18 in each group. According to this analysis, there was sufficient power to assess equivalence within bounds of \(-1 < \text{Cohen's D} < 1\). Since Cohen's D = 0.8 represents a large effect size (Cohen, 1988), we can thereby rule out large effects. While it would have been desirable to assess equivalence within more restrictive equivalence bounds, this approach is nonetheless superior to the statistically invalid approach of accepting (as opposed to failing to reject) the null hypothesis based on a nonsignificant \(P\) value in a test assessing differences.

Transparency Statement

We present the following transparency statement suggested by Simmons et al. (Simmons et al., 2012). All requirements are presented below.

We report how we determined our sample size, all data exclusions (if any), all manipulations, and all measures in the study.

Sample Size Determination

The final study sample size was determined by the number of participants included in the study when it was decided that data collection was to be concluded in 2008 and consisted of 18 patients and 18 healthy controls. No power analysis was performed before or during the study; however, a power analysis was performed prior to statistical analysis. For a 2 independent sample \(t\) test, with an alpha of 0.05, this study had 80% power to detect an effect size of Cohen's \(D = 0.96\). This corresponds to a Cohen's \(U3\) of 83% and a common language effect size of 75%. This effect is larger than we would expect, and we determined a priori that if significant, this result could likely represent a Type \(M\) error (Gelman and Carlin, 2014), and if insignificant, this result could likely represent a Type II error.

Exclusions

One PET measurement from a control subject was excluded from the analysis since it was only stored on an optical disc whose content could not be accessed. All other measurements were included in the analysis.

Measures and Analyses

The authors confirm that all ROI delineation was performed blind to the patient or control status of the subjects and that no regions other than the whole STR and the DLPFC were analyzed. All confounder checks were analyzed without testing whether they influenced the final outcome, and patient-control status was not included in any analysis other than that of ROI delineation bias, where it was the independent variable.

For transparency, we note that an exploratory SPM analysis was run on a subset of subjects during the data collection phase for which there were no significant differences between the groups using conventional statistical thresholds. Hence, there were no significant findings guiding the ROI analysis. However, due to the differences in MR modality, the fact that this analysis was not corrected for different lengths of measurement as well as the poor reliability of voxelwise estimates of cortical \([11C]\) SCH23390 BP\(_{ND}\) (Matheson et al., 2017), we do not consider these results to be valid, and this is reported solely for the purpose of transparency. In the current analysis, we restricted the a priori ROIs to the DLPFC and STR, as we have in previous studies (REF here: https://www.biorxiv.org/content/10.1101/321646v2) to reduce the potential influence of multiple comparisons to test the D1R hypothesis.

Data and Code Availability

All analysis code is available at https://github.com/matheolson/D1DNPsychosis. Due to institutional restrictions, the data cannot be shared openly within this repository. These data are pseudonymized according to national (Swedish) and EU legislation and cannot be anonymized and published in an open repository. Metadata can be openly published, and the underlying data can instead be made available upon request on a case by case basis as allowed by the legislation and ethical permits. Requests for access can be made to the Karolinska Institutet’s Research Data Office at rdo@ki.se.

Results

Demographics and Sample Characteristics

At inclusion, all patients satisfied DSM-III-R criteria for schizoaffective disorder. After 1-year follow-up, 16 patients satisfied DSM-III-R criteria for schizophrenia and 2 patients for schizoaffective disorder (Table 1). All 18 healthy controls and 15 of the patients completed the PET examination for at least 51 minutes. Two of the patients were taken out of the PET system after 33 minutes and 1 patient after 39 minutes due to anxiety. One PET measurement from a control subject was excluded from the analysis since it was only stored on an optical disc whose content could no longer be accessed.

At clinical evaluation of the T2-weighted MRI images by a radiologist, 1 patient (number 14) had a relatively large right lateral ventricle. There were no other signs of a nonpsychiatric brain disorder in this individual, and therefore this finding was not considered to be a reason for exclusion. No brain abnormalities were reported for any other subjects.
Confounder Analysis

We performed a detailed analysis of all potential confounders as described in Supplementary Materials 2. BP Vì was negatively associated with age, corresponding to previous studies (Supplementary Materials 2; Figure 1), and we therefore opted to include age in the regression models.

The lengths of the PET measurements were 33 minutes (n = 2), 39 minutes (n = 1), 51 minutes (n = 23), and 63 minutes (n = 9). We found that $[^{11}C]$SCH23390 BP Vì was not time stable and that longer measurements were associated with lower BP Vì values. We further observed that longer PET measurements were associated with lower variability, suggesting that measurement error is likely lower for longer measurements. We therefore corrected measurements to their 51-minute equivalent BPND values by removing later frames for the longer measurements and by multiplying BPND values by calibration factors calculated using the remainder of the sample for the shorter measurements. A detailed description is provided in Supplementary Materials 3.

Frequentist Analysis

In the frequentist analysis, we observed a statistically significant negative association between $[^{11}C]$SCH23390 BP Vì and age in both the DLPFC ($t = −4.66, P < .001$) and STR ($t = −3.90, P < .001$).

In the main analysis, psychosis patients had a 12.5% lower $[^{11}C]$SCH23390 BP Vì in DLPFC compared with controls relative to the mean control BP Vì value ($t = −2.30, P = .028$; Figure 1). This difference corresponds with a moderate effect size (Cohen, 1988), although the 95% confidence interval (CI) for the effect size ranged from a large negative effect to a moderate positive effect ($Hedges’ g = −0.127, 95% CI [−0.676, 0.421]$) (Cohen, 1988). Unstandardized regression coefficients are presented in Supplementary Materials 4.

In the confounder analysis presented in Supplementary Materials 2, we concluded that the 2 patients whose PET measurements were conducted with 3D data acquisition instead of 2D may potentially have biased BP Vì values and that an additional analysis should be performed with these individuals removed. Removal of these 2 individuals resulted in similar effect sizes for both regions (DLPFC: $Hedges’ g = −0.582, 95% CI [−1.132, −0.033]$. STR: $Hedges’ g = −0.131, 95% CI [−0.697, 0.434]$), suggesting that any potential influence of 2D or 3D acquisition on the main results was negligible.

The above analysis was restricted to 2 a priori ROIs to minimize the potential for false positives (Matheson et al., 2017). As requested by reviewers, we have analyzed several other regions in an additional exploratory analysis. The effect sizes for the differences between patients and controls for these regions are presented in Figure 2. The mean and standard deviation of BP Vì values within each group for each region are presented in Table 2.

Bayesian Analysis

For the Bayesian analysis, we calculated BFs, which represent the relative probability of obtaining data supporting each of the testing hypotheses, instantiated as competing models, relative to one another. For the DLPFC, we observed medium evidence supporting the decrease hypothesis over the null and strong evidence for both the null and decrease hypotheses against the increase hypothesis. For the STR, however, there was moderate evidence supporting the null hypothesis over both the increase and decrease hypotheses. The BFs are shown in Table 3.

Figure 1. Standardized residuals representing the difference between healthy controls and psychosis patients after correction for the effect of age. Significant differences were obtained for the dorsolateral prefrontal cortex (DLPFC).
Discussion

The objective of the present PET study was to compare central D1R binding between healthy control subjects and neuroleptic naive first-episode patients with schizophrenia or schizophreniform psychosis. We hypothesized higher DLPFC D1R availability in patients compared with controls. In contrast, D1R BPND in the DLPFC was significantly lower in the patients. We conclude that this effect may be regional since it was not observed for the STR, where the data were most consistent with the null hypothesis. The difference between patients and controls in the DLPFC was 12.5%, which can be viewed in relation to the recently demonstrated test-retest repeatability of about 9.5% for this tracer in the DLPFC measured using the same PET system and methodology (Stenkrona et al., 2018). The Supplementary Materials has D1R BPND values for other cortical regions as well. The effect size (Hedges’ g = 0.579) is smaller than that reported in previous studies (Table 4). However, all PET studies of the D1 receptor in schizophrenia to date have been performed with small sample sizes, which do not individually allow for the effect sizes to be estimated with a high degree of precision. Even in this study, with the largest sample of drug-naive patients yet examined, the CI around the effect size spans from very large to negligible. Comparisons of effect size magnitudes between studies are therefore highly speculative.

When reviewing the previous literature on D1R in psychosis, a pattern emerges of higher cortical D1R primarily in drug-naive patients and individuals at high risk in the majority of studies (Abi-Dargham et al., 2002, 2012; Hirvonen et al., 2006). In the only previous study finding lower levels in drug-naive patients (Okubo et al., 1997), binding potential was obtained using microparameters from 2TCM with plasma as input function. However, this method has shown low reliability for quantification of [11C]SCH23390 binding (Chan et al., 1998) due at least in part to the rapid metabolism of this tracer (Swahn et al., 1994). In the present largest sample of drug-naive patients hitherto reported in PET studies of D1R in psychosis, our analysis showed that the data were over 50 times more likely to have occurred under the decrease hypothesis model than they were under the increase hypothesis model (Table 2). It should be noted, however, that a meta-analysis of the results of the studies would...
likely result in no overall significant difference in frontal D1R
due to the heterogeneity of the results, as well as the limited
number of patients. In total there have only been 67 patients
(42 drug naïve) examined with [11C]SCH23390 and 47 patients
(19 drug naïve) examined with [11C]NNC112 (Cervenka, 2019). There
is a need for more studies in larger samples of drug-naïve pa-
tients to increase statistical power.

The lower D1R BPND found in the present sample may be due
to either a lower density (Bmax) of D1R or a lower affinity (higher
KD) or both. The Kd reflects both the affinity and the endogenous
dopamine levels. For D1R, ex vivo studies in rodents have shown
no effect on [11C]SCH23390 binding by amphetamine-induced
dopamine release or dopamine depletion (Thibaut et al., 1996),
whereas other studies found a paradoxical decrease of [11C]
SCH23390 binding in response to dopamine depletion (Guo et al.,
2003). Moreover, PET studies employing amphetamine-induced
release and reserpine-induced depletion of dopamine in NHPs
have not shown any effect on the D1R Bmax or Kd (Chou et al.,
1999). Similarly, the D1 radiotracers [11C]NNC112 (Abi-Dargham
et al., 1999) and [11C]SKF82957 (Laruelle et al., 1998) have been
reported to be insensitive to amphetamine challenge in NHP and
a study in humans did not show any effect on [11C]SCH23390
binding after DA depletion after a-methylparatyrosine (Verhoeff
et al., 2002). Hence, the present finding of a lower D1R BPND in
patients with schizophrenia is most likely due to a lower D1R
density.

One caveat when interpreting [11C]SCH23390 binding in
human cortical regions is that the values do not only represent
D1R. Studies in NHPs have demonstrated a 5HT2A contribution
to both [11C]SCH23390 and [11C]NNC112 binding in cortex of
approximately one-quarter of the binding (Ekelund et al., 2007),
the latter of which has been replicated in human studies (Slifstein
et al., 2007). In addition, some studies suggest that 5-HT2A
receptor availability may be lower in schizophrenia patients com-
pared with controls (Ngan et al., 2000; Rasmussen et al., 2010,
2016) although other centers have reported no significant dif-
ferences (Nordstrom et al., 1995; Trichard et al., 1998; Lewis et
al., 1999; Okubo et al., 2000; Erritzoe et al., 2008). However, the
magnitude of the current difference (12.5%) suggests that, if the
present findings were to be entirely accounted for by differences
in the availability of 5-HT2A receptors, they would correspond to
a 50% reduction, which is clearly larger than the reported values.
Hence, the presently observed decrease in DLPC D1R can likely
not be fully explained by a decrease in 5HT2A receptors. Similarly,
SCH23390, like all currently available pharmacological agents,
does not distinguish between D1R and D5R. However, the distri-
bution of the D5 mRNA is rare and discrete with little overlap
with the distribution pattern of the D1 mRNA (Beischlag et al.,
1995). Hence, the signal attributable to the D5R in the DLPC is
unlikely to account for the present results.

Table 4. PET Studies Comparing D1-R BPND Values in Patients With Schizophrenia or Schizophreniform Psychosis to that of Healthy Control
Subjects

| Publication                  | Subjects | Radioligand | Statistically significant differences | Hedges’ g Frontal Cortex |
|-----------------------------|----------|-------------|--------------------------------------|-------------------------|
| Okubo et al. 1997 (7)       | SCZ (DN) / HC | [11C]SCH23390 | PFC ↓                                | -1.00 (DN) / -1.39 (DF) |
| Abi-Dargham et al. 2002 (8) | SCZ (M)   | [11C]NNC112  | DLPFC ↑                               | 0.945 (DN) / 0.812 (DF) |
| Karlsson et al. 2002 (9)    | SCZ (DN) / HC | [11C]SCH23390 | no difference                         | 0.299 (DN)              |
| Hirvonen et al. 2006 (12)   | SCZ (DN) / HC | [11C]SCH23390 | CAU, PUT, CX ↓                       | -0.922 (M)             |
| Kosaka et al. 2010 (10)     | SCZ (DN) / HC | [11C]SCH23390, [11C]NNC112 | FC, ACC, TC, STR †                   | (SCH) -2.67 (M) (NNC) -2.80 (M) |
| Abi-Dargham et al. 2012 (11)| SCZ (DN) / HC | [11C]NNC112  | DLPFC, MPFC, OFC ↑ in drug naïve      | 1.03 (DN) / -0.037 (DF) |
| Poels et al. 2013 (13)      | SCZ (DN) / HC | [11C]SCH23390 | no difference                         | 1.09 (DN) / 0.154 (DF) |
| Present study               | SCZ (DN) / HC | [11C]SCH23390 | DLPFC ↓                              | -0.579 (DN)            |

Abbreviations: ACC, anterior cingulate cortex; CAU, caudate nucleus; CX, cortical regions; DF, drug free; DLPFC, dorso lateral pre frontal cortex; DN, drug naïve; FC, frontal cortex; HC, healthy control subjects; M, medicated; MPFC, medial prefrontal cortex; OFC, orbito frontal cortex; PFC, prefrontal cortex; PUT, putamen; SCZ, patients with schizophrenia or schizophreniform psychosis; STR, striatum; TC, temporal cortex. Effect size Hedges’ g (Hedges, 1981) calculated from the BPND values in frontal cortex or DLPC published in each respective study (n, mean, and SD).
have been caused by lowering the dopamine D1 transmission even further with a D1R antagonist, and that instead, a D1R agonist may have beneficial effects (Sedvall and Farde, 1995). Preclinical studies show an inverted-U dose response to D1R agonists such that there is an optimal level of D1R mediated dopamine activity on cognitive behavior (Arnsten et al., 2017). Hence, the present finding of 12.5% reduced frontal D1R may be sufficient to induce cognitive deficits and negative symptoms. Thus, in patients with reduced D1R a D1 stimulation could improve cognitive function whereas D1R antagonism may worsen symptoms. Indeed, reversal of antipsyehpic induced working memory deficits has been demonstrated in NHPs by the D1 agonist ABT 431 (Castner et al., 2000). However, an initial clinical trial failed to demonstrate improved cognition in patients with schizophrenia by the full selective D1R agonist DAR-0100A, which may have been due to low dosing and consequently also low D1R occupancy (Girgis et al., 2016). Recently, a combined haloperidol and levodopa administration, to achieve high selective D1R agonist effect, improved working memory-related brain activation in humans (van Ruitenbeek et al., 2018). Improved D1R agonists that achieve higher levels of D1R occupancy are needed to test the efficacy of this putative mechanism for cognitive enhancement in schizophrenia.

In summary, 17 healthy controls and 18 neuroleptic naïve patients with schizophrenia or schizopreniform psychosis each underwent one PET measurement with the D1R radioligand [11C]CH23390. Contrary to our hypothesis, the patients had significantly lower BPND values in the DLPFC. Although the changes in the settings of the PET acquisition and reconstruction throughout the data collection could be viewed as a limitation, our analyses show that the results are unlikely to be caused by any of the confounders. Furthermore, the magnitude of the differences suggests that they cannot be fully explained by potential decreases in 5-HT1A receptor availability.

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P.S., L.F., and C.H. designed the study. P.S. did the screening and examination of the subjects. P.S., L.F., and C.H. analyzed the data. P.S., G.J.M., S.C., and L.F. interpreted the results and drafted the article. All authors critically revised the article and approved of the final version for publication.

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**Statement of Interest**

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