Dopaminergic Activity in Antipsychotic-Naïve Patients Assessed With Positron Emission Tomography Before and After Partial Dopamine D₂ Receptor Agonist Treatment: Association With Psychotic Symptoms and Treatment Response

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ABSTRACT

BACKGROUND: Dopamine activity has been associated with the response to antipsychotic treatment. Our study used a four-parameter model to test the association between the striatal decarboxylation rate of ¹⁸F-DOPA to ¹⁸F-dopamine (k₃) and the effect of treatment on psychotic symptoms in antipsychotic-naïve patients with first-episode psychosis. We further explored the effect of treatment with a partial dopamine D₂ receptor agonist (aripiprazole) on k₃ and dopamine synthesis capacity (DSC) determined by the four-parameter model and by the conventional tissue reference method.

METHODS: Sixty-two individuals (31 patients and 31 control subjects) underwent ¹⁸F-DOPA positron emission tomography at baseline, and 15 patients were re-examined after 6 weeks. Clinical re-examinations were completed after 6 weeks (n = 28) and 6 months (n = 15). Symptoms were evaluated with the Positive and Negative Syndrome Scale.

RESULTS: High baseline decarboxylation rates (k₃) were associated with more positive symptoms at baseline (p < .001) and with symptom improvement after 6 weeks (p = .006). Subregion analyses showed that baseline k₃ for the putamen (p = .003) and nucleus accumbens (p = .013) and DSC values for the nucleus accumbens (p = .003) were associated with psychotic symptoms. The tissue reference method yielded no associations between DSC and symptoms or symptom improvement. Neither method revealed any effects of group or treatment on average magnitudes of k₃ or DSC, whereas changes in dopamine synthesis were correlated with higher baseline values, implying a potential effect of treatment.

CONCLUSIONS: Striatal decarboxylation rate at baseline was associated with psychotic symptoms and treatment response. The strong association between k₃ and treatment effect potentially implicate on new treatment strategies.

https://doi.org/10.1016/j.biopsych.2021.08.023

Striatal dopamine activity is involved in the pathophysiology of psychotic symptoms and treatment response (1,2). The literature has pointed to presynaptic dopaminergic disturbances in antipsychotic-naïve patients (2–6), while numerous studies confirm an association between blockade of striatal dopamine D₂ receptors and antipsychotic effect (7–9).

Measurements of striatal dopamine synthesis capacity (DSC) with positron emission tomography (PET) have indicated elevation in some (2,10–13) but not all (3,14–19) studies of patients with psychosis. Moreover, it has been hypothesized that treatment response is associated with dopaminergic activity (4,20). This hypothesis is supported by smaller cross-sectional studies of chronic patients (21–23), by a report of higher baseline DSC in first-episode patients responding to treatment (24), and by recent findings of reduced DSC in patients in remission as compared with healthy control (HC) subjects (25). The hypothesis is also in agreement with data showing an association between striatal and frontal availabilities of D₂ receptor in antipsychotic-naïve first-episode patients with schizophrenia and the subsequent effect of treatment (26,27).

The literature points to disturbed dopaminergic neurotransmission in the striatum and most striatal subregions as the basis of dopaminergic dysfunction and treatment response (10,11,14,24,26,28–34). The association between changes in striatal dopamine synthesis (DS) and improvement of psychotic symptoms was tested in two longitudinal studies with contradictory results (35,36). To our knowledge, no previous
studies have examined the effects of monotherapy with a partial dopamine agonist on DS and its relation to outcome. The tracer 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine (18F-DOPA) is used to measure DS in the striatum where the enzyme aromatic amino acid (or DOPA) decarboxylase is abundant, and accumulation of radioactivity is linked to the formation of radiolabeled dopamine (37). The cerebellum is considered a nonbinding region owing to the absence of the enzyme (38), justifying use of the tissue reference (TR) method as an alternative graphical analysis similar to the original Gjedde-Patlak analysis but with cerebellum as the reference region (39,40). The TR method has been applied in the majority of recent studies, probably owing to its clinical feasibility compared with methods accounting for the complex kinetics of 18F-DOPA in the brain requiring arterial blood sampling. Nevertheless, the TR method provides a relatively simplistic approximation of complex tracer kinetics (41,42). Specifically, the TR method implies at least 3 major limitations as it assumes irreversible binding, does not account for accumulation of radioactive metabolites, and depends on the validity of cerebellum as an appropriate reference region. Tracer kinetic models taking these factors into account have previously been described (40,41,43–45). The models permit calculation of individual steps in the synthesis of dopamine, including the decarboxylation rate of 18F-DOPA to 18F-dopamine (18F-DA) (k3, min−1), a key parameter. The kinetic properties of k3 are not reflected in the commonly used TR model, and no prospective studies of antipsychotic-naive patients with psychosis are available that examine k3.

Our primary aim was to study k3 in the striatum and its relationship with psychotic symptoms in lifetime antipsychotic-naive patients with psychosis and the association between striatal baseline values of k3 and symptom improvement after subsequent monotherapy with a partial dopamine D2 receptor agonist. To do this, we applied a kinetic model (henceforth referred to as the four-parameter [4P] model). To further extend the clinical relevance, baseline values of k3 were also related to changes in positive symptoms after 6 months. In addition, we compared k3 in patients and controls at baseline and looked at the potentially stabilizing effect of treatment on DS. In secondary analyses, we also focused on striatal subregions and calculated DSC (K) and its relationship with psychopathology and outcome based on both the generally used TR model (Kfl4p) and on the 4P model (K4p).

**METHODS AND MATERIALS**

**Participants**

Participants were recruited between 2015 and 2019 as part of a multimodal cohort study, PECANS II (The Pan European Collaboration on Antipsychotic Naïve Schizophrenia II), approved by the National Committee on Biomedical Research Ethics (H-3-2013-149) and previously described in detail (46–49).

Patients were referred from Mental Health Centers in the Capital Region of Denmark. Inclusion criteria were lifetime antipsychotic-naive, lifetime naive to central nervous system stimulants, 18–45 years of age, legally competent, and fulfilling the diagnostic criteria for schizophrenia, schizoaffective disorder, or nonorganic psychosis according to the International Classification of Diseases, 10th Revision, as evaluated by certified interviewers with the Schedules for Clinical Assessment in Neuropsychiatry (50). Study procedures were thoroughly explained before participants provided written informed consent. HC subjects matched on age, sex, and parental educational level were recruited through online advertising (http://www.forsgsperson.dk) with the following main exclusion criteria: first-degree relative with psychotic symptoms, lifetime psychiatric illness, or at ultrahigh risk of psychosis according to the Comprehensive Assessment of At-Risk Mental States (51). Patients were excluded in cases of involuntary admission or treatment, or treatment with antidepressants within the last 30 days. Participants were excluded if they had experienced a head injury with >5 minutes of unconsciousness, had metallic implants (not compatible with magnetic resonance imaging [MRI]), were pregnant, had a severe physical illness, or had prior substance abuse. Prescribed benzodiazepines were tolerated in patients, although not 12 hours before MRI or PET.

Treatment with the partial dopamine D2 receptor agonist aripiprazole (individual doses) was initiated upon completion of baseline examinations. Compliance was assessed by self-report and serum aripiprazole prior to PET. After the 6-week follow-up examinations, patients could switch to another compound if they experienced side effects or insufficient clinical effect. Patients experiencing intolerable side effects during the first 6 weeks were switched to another compound before follow-up and excluded from the 6-week analyses. Antidepressants were not allowed until 6-week follow-up examination was completed.

**Clinical Assessments**

Psychopathology was identified with the Positive and Negative Syndrome Scale (PANSS) (52) by trained PANSS raters. Changes in PANSS positive scores were calculated by subtracting PANSS at baseline from values at follow-up (i.e., a negative change in PANSS value indicates clinical improvement). For each subject, clinical assessments and scans were carried out within the same week at both visits.

**PET With Simultaneous Arterial Blood Sampling**

Dopaminergic metabolism was assessed with 18F-DOPA PET on an integrated PET–computed tomography scan (Siemens Biograph mCT64) from 2013. Both patients and HC subjects were PET scanned at baseline, whereas only patients had follow-up tomographies. Carbidopa 150 mg and entacapone 400 mg were administered orally 1 hour before PET to minimize 18F-DOPA metabolism before passage through the blood-brain barrier. A low-dose computed tomography scan was performed prior to all PET sessions to enable attenuation correction. Structural T1-weighted MRI scans were acquired using a 3T Philips Achieva scanner with a 32-channel head coil and used for coregistration of the PET images.

PET data were acquired in 156 frames of increasing length in two blocks lasting 1 hour each, separated by a 30-minute break. Scanning was initiated at the time of bolus infusion of 18F-DOPA. A mean dose of 334 MBq of 18F-DOPA (SD 36.7) (range: 259–432 MBq) was given intravenously. Head position at the first session was thoroughly registered and marked to
mimic initial position at the second session. A head strap was used to minimize movement.

A total of 25 arterial blood samples were collected at selected time points and counted in a gamma counter. Further samples were collected and fractionated by high-performance liquid chromatography to measure fractions of radioactive labeled 18F-DOPA and the primary metabolite 3-O-methyl-18F-DOPA (OMFD), respectively (53). Subsequently, plasma time activity curves were corrected for radioactivity originating from fractions of 18F-DOPA and OMFD. Settings, collection of arterial blood samples, and equipment are described in the Supplement.

Data Processing

The blood data and image data were processed using in-house scripts for MATLAB (R2015a [MATLAB 8.5]–R2019b [MATLAB 9.7], The MathWorks, Inc.). Image data were also analyzed with FSL (http://www.fmrib.ox.ac.uk/fsl). Time-series data were analyzed using two approaches: the nonlinear 4P model and the TR method.

First, for all datasets with arterial input, we applied the 4P model. Four parameters were fitted to the two-compartment model first described by Kumakura and Cumming (41). Calculations were performed according to Huang et al. (43), Hoshi et al. (44), and Gjedde et al. (45). This approach allowed for the determination of rate constants for both influx (K1) and efflux (K3) of intact 18F-DOPA (i.e., clearance from plasma to tissue and from tissue to plasma), decarboxylation of 18F-DOPA to 18F-DA (K4), and efflux of 18F-DA and metabolites from tissue (K6). The 4P model also accounts for the simultaneous single-compartment metabolism to OMFD. The primary outcome was the decarboxylation rate of 18F-DOPA to 18F-DA (K4). From the four parameters, we further calculated a K1 estimate (K1c) (i.e., an estimate of the net influx of 18F-DOPA, i.e., the DSC) (Supplement).

For reasons of comparability, we also used the TR method, in which cerebellum is used as a reference region under the assumption of irreversible trapping of radioactivity in the brain (44,54,55). The graphical approach yields net influx (K1c), which is supposed to be proportional to K1c, given constant 18F-DOPA kinetics (K1 and K3) in cerebellum and negligible contribution from OMFD. An overview of rate constants and equations is provided in the Supplement.

To extract activity time courses from specific anatomical regions (Figure 1), we segmented each subject’s structural MRI using FreeSurfer (https://surfer.nmr.mgh.harvard.edu). We then aligned the PET images to the structural space as described in the Supplement (see also Figure S2). Time courses were extracted from the entire striatum and from its constituents, the putamen, caudate, and nucleus accumbens (NAcc). These time courses, as well as dual arterial input functions of 18F-DOPA and 18F-OMFD, comprised the input for the 4P model, allowing an estimation of model parameters. Time courses were also extracted from cerebellum and used for the estimation of K1c using the TR method.

Statistical Analysis

Analyses were done using IBM SPSS Statistics version 25 (IBM Corp.) and the MATLAB Statistics Toolbox (R2019b, version 11.6). Demographic comparison between patients and HC subjects were performed using t tests, χ2 tests, or Fisher’s tests, as appropriate.

The primary hypotheses of associations between k3 at baseline and PANSS positive symptoms at baseline or improvement of positive symptoms after 6 weeks (or 6 mo) were investigated with the following multiple regression models.

\[
\text{PANSS}_{\text{Positive}} = \beta_0 + \beta_1k_3 + \beta_2\text{sex} + \Delta\text{PANSS}_{\text{Positive}} = \beta_0 + \beta_1k_3 + \beta_2\text{sex}
\]

Sex was included as a covariate, because we have found higher PANSS positive scores in males than in females in a previous cohort of antipsychotic-naïve first-episode patients (56).

A standard general linear model was used to test whether baseline estimates of k3 were higher in antipsychotic-naïve patients than in HC subjects. Age, sex, and smoking, which may affect dopaminergic function (53,56–58), were used as covariates in the following model:

\[
k_3 = \beta_0 + \beta_1\text{group} + \beta_2\text{age} + \beta_3\text{sex} + \beta_4\text{smoking}
\]

For the follow-up data, the effect of time was tested with a paired t test.

All analyses were performed for k3, K1c, and K1c estimates for the striatum, with a significance level of p < .05. For exploratory analyses on the putamen, caudate, and NAcc, the significance level was set to p < .017 (p < .05/3 comparisons). Information on other parameters in the 4P model is provided in the Supplement.

RESULTS

Table 1 summarizes the demographic data and clinical characteristics. There were no group differences in age, sex, ethnicity, smoking, or parental educational level, but HC subjects had, as expected, a longer education than patients (p values <.05). Tomograms were available from 31 patients and 31 HC subjects at baseline and from 15 patients after 6 weeks. Clinical examinations were available for 28 patients after 6 weeks and 15 patients after 6 months (Supplement; Figure S5). Patients were moderately ill at baseline with a PANSS total score of 77.5 (n = 31). Symptoms and function improved markedly after 6 weeks (Table S1). Mean plasma concentrations and doses of aripiprazole at 6 weeks are listed in Table S1; neither were correlated with k3 or K1c-values. All but 3 patients continued treatment with aripiprazole after 6 months.

Results of the 4P Model

Arterial blood sampling was completed in 29 patients and 27 HC subjects at baseline and in 9 patients at 6 weeks, allowing analysis using the 4P model. The patients re-examined with PET had lower baseline PANSS total and PANSS general scores than patients who were not re-examined with this method (p < .03) (n = 19).
Striatal Decarboxylation Rate ($k_3$)

At baseline, higher $k_3$ was associated with more severe positive symptoms ($\beta = 18.6, p < .001$) (Figure 2). Separated by subregion, the association was significant for the putamen ($\beta = 23.1, p = .003$) and NAcc ($\beta = 12.0, p = .013$). There was no effect of sex on baseline PANSS positive score. Table 2 lists $p$ values for the striatum and subregions.

Improvement in PANSS positive symptoms after 6 weeks was correlated with higher baseline values of $k_3$ ($\beta = -14.6, p = .006$) (Figure 2). Analyses separated by subregion yielded a significant result for the NAcc ($\beta = -11.4, p = .016$). There was no association between baseline $k_3$ and improvement of PANSS positive symptoms after 6 months. Table 3 lists $p$ values for the striatum and subregions.

We observed no group difference in $k_3$ for the striatum (Figure 3) or the striatal subregions at baseline nor any effect of age, sex, or smoking. Table 4 lists the mean values. There was no effect of time on $k_3$ for the striatum or any striatal subregion nor...
any association between change in values of $k_3$ for the striatum or any striatal subregion and change of PANSS positive score.

Mean values from additional analyses of estimates of $K_1$, $k_2$, and $k_4$, results from lateralized subregions, a correlation matrix including all parameters, and results from analyses without outliers are listed in the Supplement (Tables S2–S7). Exclusion of outliers does not change the findings.

### Dopamine Synthesis Capacity ($K_{iSP}$)

There were no associations between PANSS positive symptoms and striatal $K_{iSP}$. Analyses separated by subregion revealed an association between positive symptoms at baseline and $K_{iSP}$ for the NAcc ($\beta = 135.0, p = .003$) and at trend level for the putamen ($\beta = 78.7, p = .046$) (Table 2). Changes in PANSS positive symptoms after 6 weeks or months were not

**Figure 2.** (A) Relationship between baseline Positive and Negative Syndrome Scale (PANSS) positive score and striatal $k_3$ at baseline. Values are measured at baseline for each patient ($n = 29$). The line illustrates a simple regression between PANSS positive scores and $k_3$ with the corresponding equation: $y = 18.078x + 17.185, p = .001, r^2 = 0.34$. The regression coefficient and $p$ values are similar to the primary outcomes obtained with a multiple linear regression, correcting for sex and age (Table 2). (B) Striatal $k_3$ at baseline as predictor for change in PANSS positive scores from baseline to 6 weeks. PANSS scores were available on 26 patients at the 6-week follow-up (Table S1). The line illustrates a simple regression between $\Delta$PANSS positive scores and baseline $k_3$ with the corresponding equation: $y = -13.65x + 4.139, p = .014, r^2 = 0.23$. The regression coefficient and $p$ values differ from the primary outcomes obtained with a multiple linear regression ($p = .006$). One patient experienced worsening in positive symptoms, and 2 patients had larger improvements than the rest. In the clinic, patients responded differently to antipsychotic treatment, and the patients were kept in regression analyses.
related to baseline $K_4^{4p}$ in the striatum or any subregion (Table 3).

No baseline group difference was observed in $K_4^{4p}$ for the striatum or any subregions. There was an effect of sex on $K_4^{4p}$ in all striatal regions (all $p$ values < .017) associated with lower $K_4$ for males. There were no effects of age or smoking and any effect of time found on $K_4^{4p}$ for any regions (Table 4) or of any associations between change in $K_4^{4p}$ after treatment and effect of treatment on psychotic symptoms.

Results for TR Model

All patients and HC subjects provided data for the TR method. There were no significant baseline differences in patients who were ($n$ = 15) or were not ($n$ = 16) re-examined using the TR method.

Dopamine Synthesis Capacity ($K_4^{cer}$)

There were no associations between positive symptoms at baseline and $K_4^{cer}$ (Table 2). Changes in positive symptoms after 6 weeks or months were not related to baseline striatal $K_4^{cer}$, but we found a trend level significant association between change of PANSS positive score after 6 weeks and $K_4^{cer}$ in the NAcc ($\beta = 961.5, p = .018$) (Table 3).

No baseline group difference of estimates of $K_4^{cer}$ was observed for the striatum or any subregions (Table 4). In exploratory analyses, we found an effect of sex on $K_4^{cer}$ for the NAcc ($\beta = -0.001, p < .005$) but no effect of age or smoking. No effect of time was found on $K_4^{cer}$ in any regions, nor did we see an association between change in $K_4^{cer}$ after 6 weeks and change in the PANSS positive score in any striatal region.

High striatal baseline DS values were associated with more pronounced decreases in DS from baseline to follow-up. This was found for $K_4^{cer}$ in the striatum ($r_{13} = -0.676, p = .006$) and additionally in some subregions for $k_3$ and $K_4^{4p}$ (Supplemental Results).

DISCUSSION

To our knowledge, this is the first prospective study of striatal decarboxylation rate in antipsychotic-naïve patients with first-episode psychosis, the first to evaluate the effect of a partial dopamine $D_2$ receptor agonist treatment on DS, and the first comparison of the 4P and TR methods. Our main hypotheses on associations between striatal decarboxylation rate of DOPA to DA ($k_3$) at baseline and positive symptoms, as well as the effect of 6 weeks of treatment on these symptoms, were confirmed, supporting that the activity of the enzyme DOPA decarboxylase plays a key role in psychosis. The relationship between baseline $k_3$ and antipsychotic effect was not present after 6 months, most likely because of lack of power at this time. A hypothesis $k_3$ were not elevated in patients compared with HC subjects.

Exploratory analyses of correlations between psychotic symptoms and $k_3$ in striatal subregions revealed a significant association in the putamen. We did not further subdivide the putamen and speculate whether the relationship may be driven by $k_3$ estimates for the precommissural putamen, which is part of the associative striatum (31). The data similarly pointed to associations between $k_3$ for the NAcc and positive symptoms, as well as improvement of these symptoms. Generally, the literature has pointed to the caudate, or functionally, the associative striatum, as the subregions involved in dopaminergic dysfunction and treatment response (26,29,31), but preclinical studies (32,34,59) and clinical data similarly have implicated the NAcc (12,30,60) and putamen (10,11,14).

| Region                  | $k_3, n = 29$ | $K_4^{4p}, n = 29$ | $K_4^{cer}, n = 31$ |
|-------------------------|--------------|-------------------|---------------------|
|                         | $\beta$ Value | $p$ Value         | $\beta$ Value       | $p$ Value         | $\beta$ Value | $p$ Value         |
| Striatum                | 18.646       | .001 a            | 67.959              | .094              | -527.823      | .285              |
| Putamen                 | 23.066       | .003 a            | 78.682              | .046              | -506.628      | .241              |
| Caudate                 | 7.074        | .073              | 36.272              | .384              | -375.043      | .517              |
| Nucleus Accumbens       | 11.978       | .013 a            | 134.997             | .003 a            | -516.809      | .250              |

*Significant results. Significance level is .05 for the whole striatum and .017 for analyses on striatal subdivisions.

Table 2. Association Between Baseline Dopamine Activity Measured With the Four-Parameter Model ($k_3$ and $K_4^{4p}$) and Tissue Reference Method ($K_4^{cer}$) and Positive Symptoms at Baseline

| Region                | $\Delta$PANSS$_{pos, 6WFU}$ |
|-----------------------|-----------------------------|
|                       | $k_3, n = 26$ | $K_4^{4p}, n = 26$ | $K_4^{cer}, n = 28$ |
|                       | $\beta$ Value | $p$ Value | $\beta$ Value | $p$ Value | $\beta$ Value | $p$ Value |
| Striatum               | -14.641       | .006 a    | -44.705       | .321      | 448.238       | .324      |
| Putamen                | -9.567        | .233      | -44.705       | .302      | 441.265       | .265      |
| Caudate                | -4.901        | .201      | -40.878       | .397      | 154.963       | .778      |
| Nucleus Accumbens      | -11.662       | .013 a    | -47.080       | .402      | 961.475       | .018      |

*Significant results. Significance level is .05 for the whole striatum and .017 for analyses on striatal subdivisions.
For comparison, we also included analyses of DSC for the
4P (K_{4p}) and TR (K_{4p}) methods. These analyses revealed no
increased estimates of K_{4p} or K_{cer} for patients compared with
HC subjects nor any effect of time or any associations among
K_i and psychopathology or treatment effect, but K_{cer} values
and K_{4p} values in some subregions) at baseline were
correlated with change. Exploratory analyses of K_{4p} in the
striatal subregions did show an association between baseline
K_{4p} for the NAcc and psychotic symptoms and a tendency for
associations in the putamen, further implicating the role of
dopaminergic activity in the NAcc and putamen in the
psychopathology of patients.

The only previous prospective study of the association
between baseline dopamine activity and treatment response in
patients with first-episode psychosis included 26 patients, 14
of whom were antipsychotic naïve (24). Jauhar and colleagues
found a correlation between K_{cer} and improvement of PANSS
positive symptoms after 4 weeks of treatment with different
antipsychotics. Isolated to the NAcc, we detected a trend-level
association between K_{cer} and improvement of PANSS positive
symptoms after 6 weeks, while the association was significant
when k_3 was applied. In agreement with the present estimates
of K_{cer}, the authors found no relationship between
psychotic symptoms and K_{cer} at baseline, while we observed such an association for K_{4p} in the NAcc. In a cross-sectional study of
striatal K_{cer} for 22 patients with bipolar disorder and 16 pa-
tients with schizophrenia, the same group reported a
association between DSC and psychotic symptoms in the
whole group of patients and in patients with bipolar disorder
but not in the subgroup of patients with schizophrenia. The
authors suggested that the latter was due to lack of power or
the inclusion of more treated patients with schizophrenia (61).
We were, however, unable to show such an association after
applying the TR method to a sample of 31 antipsychotic-naïve
patients.

The apparent discrepant sensitivity of the TR method in
various studies can be explained by different patient pop-
ulations as well as by different methodologies. The current
study included a group of 31 strictly antipsychotic-naïve pa-
tients, all within the schizophrenia spectrum, whereas 10 of the
26 patients in Jauhar et al.’s (24) study were diagnosed with
bipolar affective disorder. The literature points to comparable
disturbances in dopamine activity in bipolar and schizophrenia
spectrum disorders (13), but given the complexity of psychotic
disorders, subgroups are likely to exist (62), and a recent meta-
analyses of striatal dopamine function found significant heter-
geney in striatal dopamine activity in schizophrenia (6). Other
differences between the studies include treatment regi-
mens, striatal regions of interest, and the tomography method
used.

In agreement with the present results, Jauhar and col-
leagues (36) did not find any effect of (naturalistic) antipsy-
chotic treatment on striatal DSC in 17 first-episode patients,
nor did they see an association between changes in DSC and

Table 4. Mean Values of Decarboxylation Rate (k_3) and Dopamine Synthesis Capacity From the Four-Parameter Model (K_i^{4p}) and the Tissue Reference Method (K_i^{cer}) in Patients With FEP and HC Subjects

| Region       | Mean k_3 Value min^{-1} | Mean K_i^{4p} Value mL × g^{-1} × min^{-1} | Mean K_i^{cer} Value mL × g^{-1}/min |
|--------------|-------------------------|--------------------------------------------|-------------------------------------|
|              | HC Subjects, n = 27     | FEP BL, n = 29                             | FEP FU, n = 9                        | HC Subjects, n = 31                 | FEP BL, n = 31                             | FEP FU, n = 15                             |
| Striatum     | 0.220 (0.224)           | 0.129 (0.113)                              | 0.139 (0.039)                        | 0.026 (0.009)                       | 0.024 (0.021)                              | 0.024 (0.003)                              | 0.010 (0.002) | 0.010 (0.001) | 0.010 (0.000) |
| Putamen      | 0.355 (0.403)           | 0.204 (0.163)                              | 0.113 (0.032)                        | 0.054 (0.019)                       | 0.049 (0.017)                              | 0.025 (0.003)                              | 0.010 (0.002) | 0.010 (0.001) | 0.011 (0.000) |
| Caudate      | 0.536 (0.463)           | 0.454 (0.322)                              | 0.195 (0.039)                        | 0.049 (0.017)                       | 0.047 (0.015)                              | 0.024 (0.002)                              | 0.009 (0.002) | 0.009 (0.001) | 0.009 (0.000) |
| Nucleus      | 0.380 (0.317)           | 0.367 (0.297)                              | 0.139 (0.038)                        | 0.046 (0.018)                       | 0.337 (0.297)                              | 0.021 (0.003)                              | 0.006 (0.001) | 0.006 (0.001) | 0.007 (0.001) |
| Accumbens    |                         |                                            |                                      |                                    |                                            |                                      |                                    |

Values are presented as mean (SD).
BL, baseline; FEP, first-episode psychosis; FU, 6-week follow-up; HC, healthy control.
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treatment effect. In contrast, Gründler et al. (35) found a decrease in the relative activity of DOPA decarboxylase in 9 initially medication-free patients after haloperidol treatment. A previous study on the effect of a single dose of aripiprazole in healthy men suggested that aripiprazole would stabilize DSC (63). We confirm this in the present prospective study. The studies differ with regard to patient samples, choice of treatment, and imaging and analytic methods, but Jauhar et al. (36) did not detect such a normalization of K1cex. Taken together with our finding of no effect of treatment on DSC on a group level and no association between change in DSC and psychopathology, a normalization of DSC as the mechanism of action for second-generation compounds or partial D2 receptor agonists is still debatable.

The present estimates revealed no increased values for k3, K1dp, or K1cex for patients compared with HC subjects. Given the potential influence of antipsychotic medication and course of illness on DS, prospective studies on antipsychotic-naive patients are critical to the exploration of neurochemical disturbances. These patients are hard to recruit, and previous studies are generally characterized by small or mixed patient samples and mixed results. So far, only one group studied DSC in exclusively antipsychotic-naive patients in an overlapping sample (n = 7–10) (11,14), where they found increased DSC in the patients. Other studies included subgroups of antipsychotic-naive patients (n = 2–14) (10,24,61,64). In agreement with the present results, the largest of these studies (n = 28, of whom 12 were antipsychotic naïve) did not reveal different estimates of DSC in patients and HC subjects (64), whereas the aforementioned longitudinal study from the same group reported increased K1cex in a mixed sample of patients with bipolar disorder or schizophrenia, of which the majority had bipolar disorder (24).

Sex differences may have influenced the results (21,56). In contrast to the present study, most previous studies included an excess of male patients, and we observed an effect of sex contrast to the present study, most previous studies included subgroups of antipsychotic-naive patients with psychosis were associated with more severe psychotic symptoms at baseline and subsequent treatment response. The 4P model appears to be more sensitive in terms of detecting associations between presynaptic dopaminergic activity and psychosis compared with the more commonly used TR method. The association between high baseline K1cex values (and k3 and K1dp values in some subregions) and larger changes support the notion that these compounds may stabilize presynaptic dopaminergic activity. The strong association between the estimates of k3 and treatment effect has implications for the development of new treatment strategies, but further studies of the proper modeling of the uptake and metabolism of 18F-DOPA in longitudinal studies on initially antipsychotic-naive patients are needed.

Conclusions

Using a 4P model, we showed that high striatal decarboxylation rates of DOPA to DA (Kd) in antipsychotic-naive patients with psychosis were associated with more severe psychotic symptoms at baseline and subsequent treatment response. The 4P model appears to be more sensitive in terms of detecting associations between presynaptic dopaminergic activity and psychosis compared with the more commonly used TR method. The association between high baseline K1cex values (and k3 and K1dp values in some subregions) and larger changes support the notion that these compounds may stabilize presynaptic dopaminergic activity. The strong association between the estimates of k3 and treatment effect has implications for the development of new treatment strategies, but further studies of the proper modeling of the uptake and metabolism of 18F-DOPA in longitudinal studies on initially antipsychotic-naive patients are needed.

ACKNOWLEDGMENTS AND DISCLOSURES

This study was funded by Ph.D. grants and a postdoc grant from the Mental Health Services in the Capital Region of Denmark (to AKS, KT, and MØN), a Ph.D. grant from the Faculty of Health and Medical Sciences, University of Copenhagen (to KBS), an independent grant from the Lundbeck Foundation to the Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (Grant No. R155-2013-16337 [to BYG]), grants from the Worzner Foundation (to AKS) and Gerhard Lind Foundation (to AKS), and support from the Mental Health Services, Capital Region of Denmark (to BYG).

The funding sources played no role in the design or conduction of the study design, nor in the collection, analysis, and interpretation of data, nor in the writing, review approval, and submission of the manuscript for publication.

We wish to thank the staff at the Center for Neuropsychiatric Research and Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, especially Gitte Saltoft, Helle Schabel, Kasper Jessen, and Mikkel Erlang, at the PET center, University Hospital Herlev, especially Tri Hien Viet Huyhn, Nina Tietgen, and Sofie Pilgaard, without whom the PET procedures could not have been carried out. In addition, we thank Functional Imaging Unit—Rigshospitalet. Claus Svarer and Lars Pindborg from Neurobiology Research Unit—Rigshospitalet for fruitful discussion on methods.

BYG is the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research, which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. All grants are the property of the Mental Health
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Services in the Capital Region of Denmark and administered by them. BHE received lecture fees and/or is part of the advisory board at Bristol-Myers Squibb, Eli Lilly and Company, Janssen-Cilag, Otsuka Pharma Scandinavia AB, Takeda Pharmaceutical Company, Boehringer Ingelheim, and Lundbeck Pharma A/S. All other authors report no biomedical financial interests or potential conflicts of interest.

ClinicalTrials.gov: The Pan European Collaboration on Antipsychotic Naive Schizophrenia II (PECANSII); [https://www.clinicaltrials.gov/ct2/show/NCT02339847?term=Glnth%5C3%5B8] &cond=Schizophrenia&rank=7; NCT02339844.

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Received Mar 10, 2021; revised and accepted Aug 30, 2021. Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.08.023.

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