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RESEARCH ARTICLE

Frontal $D_{2/3}$ Receptor Availability in Schizophrenia Patients Before and After Their First Antipsychotic Treatment: Relation to Cognitive Functions and Psychopathology

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Abstract

Background: We have previously reported associations between frontal $D_{2/3}$ receptor binding potential positive symptoms and cognitive deficits in antipsychotic-naïve schizophrenia patients. Here, we examined the effect of dopamine $D_{2/3}$ receptor blockade on cognition. Additionally, we explored the relation between frontal $D_{2/3}$ receptor availability and treatment effect on positive symptoms.

Methods: Twenty-five antipsychotic-naïve first-episode schizophrenia patients were examined with the Positive and Negative Syndrome Scale, tested with the cognitive test battery Cambridge Neuropsychological Test Automated Battery, scanned with single-photon emission computerized tomography using the dopamine $D_{2/3}$ receptor ligand [^{123}I]epidepride, and scanned with MRI. After 3 months of treatment with either risperidone (n = 13) or zuclopenthixol (n = 9), 22 patients were reexamined.

Results: Blockade of extrastriatal dopamine $D_{2/3}$ receptors was correlated with decreased attentional focus (r = -0.615, P = .003) and planning time (r = -0.436, P = .048). Moreover, baseline frontal dopamine $D_{2/3}$ binding potential and positive symptom

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reduction correlated positively ($D_{2/3}$ receptor binding potential left frontal cortex rho = 0.56, $P = .003$; $D_{2/3}$ receptor binding potential right frontal cortex rho = 0.48, $P = .016$).
Conclusions: Our data support the hypothesis of a negative influence of $D_{2/3}$ receptor blockade on specific cognitive functions in schizophrenia. This is highly clinically relevant given the well-established association between severity of cognitive disturbances and a poor functional outcome in schizophrenia. Additionally, the findings support associations between frontal $D_{2/3}$ receptor binding potential at baseline and the effect of antipsychotic treatment on positive symptoms.

Keywords: Schizophrenia, antipsychotic-naïve, epidepride, SPECT, frontal dopamine $D_{2/3}$ receptor, psychopathology, cognition

Introduction

The literature generally supports an association between psychotic symptoms and both increased synthesis and release of dopamine in the associative striatum (Howes et al., 2012). Clinical and preclinical data additionally point to a key role of prefrontal dopamine activity for schizophrenic symptomatology, including cognitive deficits as well as psychopathology (Knable and Weinberger, 1997; Glenthoj et al., 2006; Floresco, 2013; Fagerlund et al., 2013; Arnsten, 2013). We have previously shown associations between frontal $D_{2/3}$ receptor binding potential (BP_{ND}) values and cognitive measures of planning, attention, and set shifting in antipsychotic-naïve first-episode schizophrenia patients (Fagerlund et al., 2013). The data indicated that in schizophrenia patients, frontal dopamine $D_{2/3}$ receptors are involved in cognition to a higher degree than in healthy subjects and that patients depend on frontal $D_{2/3}$ availability for normal cognitive processing. Moreover, in the same cohort of antipsychotic-naïve patients, we additionally found a significant, positive correlation between BP_{ND} and psychopathology (Glenthoj et al., 2006).

Our clinical in vivo data on extrastriatal $D_{2/3}$ receptors (Glenthoj et al., 2006; Fagerlund et al., 2013) as well as corresponding clinical in vivo data on extrastriatal D_1 receptors (Abi-Dargham et al., 2002, 2012) are generally in agreement with the so-called two-state dynamic model of dopamine function in PFC proposed by Seamans and Yang (2004). The model suggests that predominant D_1 receptor activation will increase the inhibition of intruding stimuli (closure of the gate), and initiation and stabilization of goal-related representations in working memory. In this way, D_1 activation will enhance the robustness of working memory by facilitating the encoding of specific stimuli at the expense of other internally or externally derived representations. The authors call this network state 2. In contrast, the functional state with an open gate is denoted network state 1. In state 1, predominant D_2 activity will reduce inhibition, which will allow multiple inputs to be represented at the same time. State 1 allows the organism to react upon important stimuli, but a switch to state 2 is necessary to avoid "contamination" of information processing by externally or internally derived distracters. Hence, Seamans and Yang (2004) propose that increased prefrontal D_2 receptor activity result in random, tangential, or intrusive thoughts and development of positive psychotic symptoms. Our previous data support the clinical relevance of $D_{2/3}$ receptor activity for state 1 in the model (Glenthoj et al., 2006; Fagerlund et al., 2013).

In the present study, we related blockade of frontal $D_{2/3}$ receptors to cognitive functions. Based on our previous data (Fagerlund et al., 2013), we expected high occupancy to further compromise selected cognitive functions. Additionally, we explored if higher BP_{ND} at baseline (Glenthoj et al., 2006) was associated with more pronounced reductions in positive psychotic symptoms.

Methods and Materials

The study was approved by the ethical committee of Copenhagen and Frederiksberg (KF 01-078/97 and 01-012/98). After complete description of the study, written informed consent was obtained.

Participants

Patients were included if fulfilling criteria for the international classification of diseases 10th version (ICD-10) for schizophrenia. The diagnosis was confirmed by a trained psychiatrist using Schedules for Clinical Assessment in Neuropsychiatry 2.0 (Wing et al., 1990). This was the first admission for treatment of psychotic symptoms for all patients, and none had been exposed to antipsychotic medication at the baseline examinations. Only antipsychotic-naïve patients were included. Patients with known retardation or who were compulsorily hospitalized were excluded (Glenthoj et al., 2006; Fagerlund et al., 2013). Patients received antipsychotic medication within normal clinical range during the treatment period (Table 1).

Baseline data relating BP_{ND} to cognitive functions or psychopathology in the same cohort of antipsychotic-naïve patients and matched healthy controls have previously been reported (Glenthoj et al., 2006; Fagerlund et al., 2013) as have longitudinal single-photon emission computerized tomography (SPECT) data on [^{123}I]epidepride binding to cerebellar receptors (Pinborg et al., 2007). In addition, we have reported longitudinal and/or baseline data on disturbances in sensorimotor gating, structural correlates of sensorimotor gating, brain structure, and cognitive data on patients compared with matched controls in the same cohort of patients and controls (Mackeprang et al., 2002; Fagerlund et al., 2004, 2013; Glenthoj et al., 2007; Hammer et al., 2011, 2013).

Medication

Patients were randomly allocated to either zuclopenthixol or risperidone treatment. Medication dose was individually determined based on the severity of symptoms and reported adverse effects. The use of benzodiazepines was allowed but restricted on days of examinations. The study is part of a longitudinal cohort study. When the study was originally planned, we expected, but did not find, differential effects of first- and second-generation antipsychotic compounds on cognitive functions and sensory motor gating (Mackeprang et al., 2002; Fagerlund et al., 2004). Risperidone and zuclopenthixol were chosen because at that time they were the most commonly used first- and second-generation antipsychotic compounds in Denmark, respectively. Based on our previous observations, we did not expect differential effects of the two compounds with respect to neither cognition nor psychopathology nor frontal $D_{2/3}$ receptor occupancy.

Table 1. Demographics, Clinical Ratings, and Treatment

	All Patients (n = 25)	Zuclopenthixol (n = 9)	Risperidone (n = 16)
Age	26.5 (5.0)	26.3 (5.2)	27.2
Sex M/F	18/7	6/3	12/4
DUP (months)	19.4 (18.2)	15.3 (8.0)	21.7 (21.9)
PANSS Baseline			
Positive	20.2 (3.9)	18.4 (2.3)	21.2 (4.3)
Negative	19.6 (5.3)	17.8 (5.1)	20.6 (5.3)
Total	70.0 (12.6)	64.4 (12.3)	73.1 (12.1)
PANSS follow-up			
Positive	10.4 (2.2)	9.7 (1.9)	10.9 (2.3)
Negative	16.5 (3.4)	15.3 (2.9)	17.1 (3.6)
Total	47.7 (6.1)	19.8 (2.3)	21.0 (2.9)
PANSS change			
Positive	9.76 (3.2)**	8.78 (2.2)**	10.31 (3.6)**
Negative	3.12 (4.4)**	2.44 (3.5)	3.50 (4.9)**
Total	22.24 (10.6)**	19.67 (10.7)**	23.69 (10.6)**
Treatment period, wk	12.6 (3.4)	12.8 (4.2)	12.5 (3.0)
Medication dose, mg		9.6 (6.3) [4–26]	3.8 (1.7) [1–7]
Extrastriatal occupancy	65%	66%	65%

Abbreviations: DUP, duration of psychosis; PANSS, Positive and Negative Syndrome Scale.
Variables are provided in mean values. Standard deviations are provided in () and range in []. Significant differences between groups are marked with*, $P < .05$. Significant changes in PANSS score over time are marked with **, $P < .05$. There were no other significant differences between groups.

Psychopathology and Cognition

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Cognitive measures were obtained with Cambridge Neuropsychological Test Automated Battery (CANTAB) (Sahakian and Owen, 1992; Lowe and Rabbitt, 1998). For the present analyses, we a priori selected a total of 7 cognitive measures addressing domains of attention, executive function, and processing speed (Fagerlund et al., 2004, 2013). Selected cognitive measures were CANTAB Rapid visual information processing; CANTAB Stockings of Cambridge minimal number of moves; CANTAB Stockings of Cambridge initial thinking time; CANTAB Stockings of Cambridge subsequent thinking time; CANTAB intra extra dimensional set shifting task; Verbal semantic fluency; and Trail making B (minus A).

SPECT

SPECT scans were performed using a Tomomatic 232 scanner (Medimatic, Copenhagen), a fast rotating (6 rpm), brain-dedicated SPECT scanner that simultaneously recorded radiation from 2 parallel, trans-axial slices of the brain with a slice thickness of 17 mm and distance between mid-slice levels of 10 mm. Four recording sessions of 15 minutes began approximately 6 hours after the bolus injection. Data were then achieved from 8 orbitomeatal (OM) planes covering the brain from OM +20 to OM +90, generating 8 slices. The spatial resolution in the trans-axial plane was 12 mm full width half maximum (FWHM). The energy window was set to 140 to 180 KeV. For quantification of $D_{2/3}$ receptors in extrastriatal regions, we used [^{123}I]epidepride (Kessler et al., 1991) and a bolus/infusion approach (Pinborg et al., 2000). Tracer steady-state conditions were obtained in extrastriatal regions within 3 to 4 hours, but the infusion continued for 7 hours to minimize individual differences in plasma clearance and binding parameters. A 64 x 64 filtered back-projection reconstruction matrix was used to reconstruct data. The trans-axial slices were corrected with a uniform attenuation coefficient of 0.05 cm^{-1}. Subjects received approximately 150 MBq [^{123}I]epidepride (MAP, Medical Technologies, Inc., Finland) per examination. The radiochemical purity was >99% and the specific activity >1.8 x 10^{14} Bq/nmol.

MRI

At baseline, high-resolution 3D T1-weighted sagittal MPRAGE scans of the whole head were acquired for structural analyses. Twenty-two patients were examined on a 1.5 Tesla Siemens Vision scanner (TE = 4 ms; TR = 9.7 ms; flip angle = 12°; matrix = 256 x 256; FOV = 250 mm; 0.98 x 0.98 x 1 mm voxels; 170 slices). Three patients were scanned on a 1.0 Tesla Siemens Impact scanner (TE = 4.4 ms; TR = 11.4 ms; flip angle = 15°; matrix = 256 x 256; FOV = 250 mm; 0.98 x 0.98 x 1 mm voxels; 170 slices). Patients had no clinically significant brain pathology as determined by neuroradiological examination.

Coregistration

Coregistration between SPECT and MRI images was performed using a Matlab (Mathworks Inc., Natick, MA) based semiautomatic program, Interactive Point Selection (Willendrup et al., 2004). For each image modality, at least 6 corresponding anatomical points were manually identified. A rigid transformation of the images was estimated automatically by minimizing the sum of squared errors between the defined points. Using the identified rigid transformation matrix, the MRI images were resliced to the planes defined by the SPECT images (10 mm between slices and an in-plane resolution of 1 x 1 mm as in the MRI images).

Region of Interest

A set of 6 anatomical regions of interest (ROIs) (left and right frontal cortex, left and right temporal cortex, and left and right cerebellum) were manually delineated at 2D transverse MRI planes using a locally developed Matlab (Mathworks Inc., Natick, MA) based program (editroi) (Figure 1). ROIs were identified by means of a neuroanatomical atlas (Talairach and Tournaux, 1988,

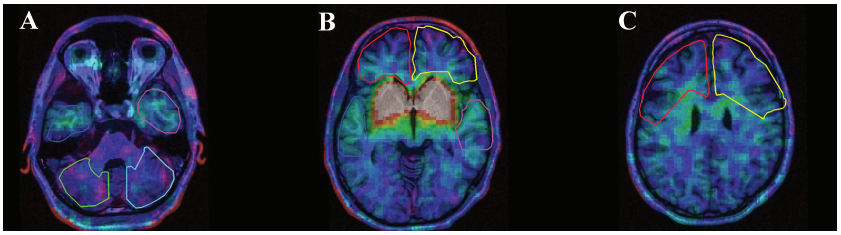

Figure 1. Example of axial image coregistration of single-photon emission computerized tomography (SPECT) and magnetic resonance (MR) images in a patient. Regions delineated are: (A) cerebellum (left in green and right in turquoise); (B) temporal cortex (left in blue and right in purple); (C) frontal cortex (left in red and right in yellow). SPECT spatial resolution in the trans-axial plain was 12 mm full width half maximum (FWHM) with a 17-mm slice thickness. MR images were resliced to the planes defined by the SPECT images giving an in-plane resolution of 1 x 1 mm in the MRI images and 10 mm between slices.

MNI). Subsequently, ROIs were applied to the SPECT images, and mean counts of the voxels included in each of the ROIs were extracted. BP_{ND} was calculated for left and right frontal cortex, left and right temporal cortex, and left and right cerebellum.

Quantification of Dopamine D_2 Receptors

The BP_{ND} was used as a measure of regional $D_{2/3}$ receptor availability before and after treatment (Innis et al., 2007). $BP_{ND} = \frac{VT - VND}{VND}$, where V_T is the total volume of distribution of [^{123}I]epidepride in a ROI and V_{ND} represents the volume of distribution of nondisplacable [^{123}I]epidepride in tissue. Cerebellum is used as a representation of nondisplaceable [^{123}I]epidepride binding (Glenthoj et al., 2006). For the calculation of extrastriatal $D_{2/3}$ receptor occupancy, we used the paired distribution volumes before and after treatment. This was done using the paired distribution volumes before (the unblocked situation) and after treatment (the partially blocked situation) and the Lassen Plot (Lassen et al., 1995). For each patient, a Lassen Plot was generated, including the regions left and right frontal cortex, left and right temporal cortex, and left and right cerebellum. Occupancy was then calculated from the slope of the Lassen plot using linear regression analysis and provides a measure of extrastriatal $D_{2/3}$ occupancy.

Statistical Analyses

All data analyses were performed using the statistical analysis software, SPSS 20 (SPSS, Statistics 20, IBM Corporation, Armonk, NY). Both in the complete dataset and in the 2 treatment groups, separately, the BP_{ND} and occupancy data object variables could be fitted approximately by normal distribution for all ROIs (Glenthoj et al., 2006). Differences in occupancy between treatment groups were consequently tested using ANOVA techniques. Change scores in psychopathology (follow-up minus baseline) were calculated separately for PANSS positive, negative, and total scores. PANSS scores were not normally distributed and consequently, group differences were tested using nonparametric techniques, for example, the Mann-Whitney *U* test, and changes over time were tested with Wilcoxon signed rank test. The Spearman's rank-correlation coefficient was used to test potential associations between PANSS score, BP_{ND}, and occupancy.

Most of the cognitive measures could be fitted immediately by normal distribution and if not, a log transformation was applied to improve fit. Changes in cognitive function (follow-up minus baseline) were calculated for all 7 variables. Our measurement of change in cognitive variables was also analyzed using the residuals from a regression analysis of endpoint on baseline values, predicting endpoint from baseline. Possible associations between occupancy and cognitive function were tested using correlation analysis in accordance with the statistical properties of the variables. Since previous data have shown the need for extending linear analysis through possible quadratic associations, both occupancy and squared occupancy measures were used in the analyses. Potential (gender x occupancy) and (medication group x occupancy) interaction effects for both occupancy and occupancy squared measures were tested.

Results

Demographic and Clinical Data

Twenty-five patients (18 males, 7 females) entered the study. After baseline examinations, 9 patients were randomized to treatment with zuclopenthixol and 16 were allocated to risperidone. Twenty-two patients (16 males, 6 females) completed follow-up examinations; however, 1 of the patients (male) did not go through the cognitive examination but completed all other tests. Two patients (1 male, 1 female) were excluded from follow-up examinations because of compulsorily hospitalization. One patient (male) was excluded from follow-up analyses due to incomplete SPECT data. All 3 excluded patients were treated with risperidone. No significant differences in demographic, clinical, and neurochemical variables between dropouts and completers were found. The 2 patient groups were comparable regarding age, gender, treatment period, and mean duration of psychosis (Table 1).

Patients were moderately ill, and psychopathology improved significantly in the whole group and in the risperidone group during treatment. Improvement in negative symptoms was only trend level in the zuclopenthixol group (Table 1).

Extrastriatal Dopamine $D_{2/3}$ Receptor Occupancy

Mean extrastriatal $D_{2/3}$ receptor occupancy in the whole group was 65% (n = 22, range 31–88%, spearman correlation r = 0.94); 66% (n = 9, range 52–76%, r = 0.95) in the zuclopenthixol group; and 65% (n = 13, range 31–88%, spearman correlation r = 0.93) in the risperidone group. There was no significant difference in occupancy between groups (Table 1). In the risperidone group, dose and extrastriatal occupancy were significantly correlated (n = 13, r = 0.68, *P* = .01) (Figure 3A) but not in the zuclopenthixol group (*P* > .2) (Figure 3B).

Extrastriatal Dopamine $D_{2/3}$ Receptor Occupancy and Cognition

For all patients, extrastriatal $D_{2/3}$ receptor occupancy showed a significant negative correlation with planning time at follow-up (Stockings of Cambridge initial thinking time, n = 21, r = -0.436, *P* = .048) (Figure 4a). Moreover, occupancy and improvement in

attention from baseline to follow-up was negatively correlated in the whole group (signal detection measure A' from the Rapid Visual Information Processing test, n = 21, r = -0.615, $P = .003$) (Figure 4b). In the zuclopenthixol group, we found a significant negative correlation between occupancy and attention at follow-up (signal detection A' from the Rapid Visual Information Processing test, n = 9, rho = -0.795, $P = .018$) and at a trend level with planning latency also at follow-up (Stockings of Cambridge initial thinking time, n = 9, r = -0.70, $P = .050$). In the risperidone group, a significant negative correlation between occupancy and improvement in attention was found (signal detection A' from the Rapid Visual Information Processing test, n = 13, r = -0770, $P = .003$). Even when using 2 different statistical methods, the overall results remained the same regardless of method.

Extrastriatal Dopamine $D_{2/3}$ Receptor Occupancy and Psychopathology

No significant associations were found between extrastriatal dopamine $D_{2/3}$ receptor occupancy and improvement in PANSS positive symptoms for the whole group. Separate analyses of the 2 treatment groups did not alter the results.

Frontal Dopamine $D_{2/3}$ Receptor Availability and Treatment Response

In the total patient group, we found significant positive correlations between BP_{ND} in frontal cortex bilaterally and improvement in positive symptoms (Figure 2) (BP_{ND} in left frontal cortex $P = .003$, rho = 0.56; BP_{ND} right frontal cortex $P = .016$, rho = 0.48). In the risperidone group, similar significant positive correlations between BP_{ND} in frontal cortex and improvement in positive symptoms were found (BP_{ND} left frontal cortex $P = .007$, rho = 0.64; BP_{ND} right frontal cortex $P = .002$, rho = 0.71) though not in the zuclopenthixol group ($P > .4$).

Discussion

In the present study, we related blockade of frontal $D_{2/3}$ receptors to cognitive functions and examined whether higher BP_{ND} at baseline was associated with reductions in positive psychotic symptoms. Our results showed that extrastriatal dopamine $D_{2/3}$ receptor blockade was correlated with decreased attentional focus and planning time. Moreover, baseline frontal dopamine $D_{2/3}$ BP_{ND} was positively correlated with positive symptom reduction. In line with our hypothesis, the data support that blockade of extrastriatal dopamine D2/3 receptors may further compromise specific cognitive functions in initially antipsychotic-naïve first-episode schizophrenia patients. The negative associations between occupancy and both attention at follow-up and improvement of attention scores further support a possible detrimental effect of high dopamine blockade on attention. The significant negative associations to follow-up scores on planning latency could in itself suggest a beneficial effect of high occupancy levels on planning, but since patients perform worse than healthy controls on planning efficiency both at baseline and follow-up, faster planning latencies do not indicate improved processing in lieu of improved planning. This suggests that faster planning latencies at follow-up were not advantageous, but rather indicate a lack of sufficient planning (Fagerlund et al., 2013). Even so, most of the cognitive tests were not related to $D_{2/3}$ receptor blockade. Our results are in accordance with other findings suggesting that antipsychotics may worsen aspects of attention (Tost et al., 2006) and decision-making (Eisenegger et al., 2014) in healthy volunteers.

As expected, the variables significantly affected by blockade of frontal $D_{2/3}$ receptors were the variables that in the baseline data showed quadratic associations with $D_{2/3}$ BP_{ND} in line with an inverted U-curve (Fagerlund et al., 2013). This indicates that blockade of frontal $D_{2/3}$ receptors by antipsychotics may worsen some cognitive domains following an inverted U-curve,

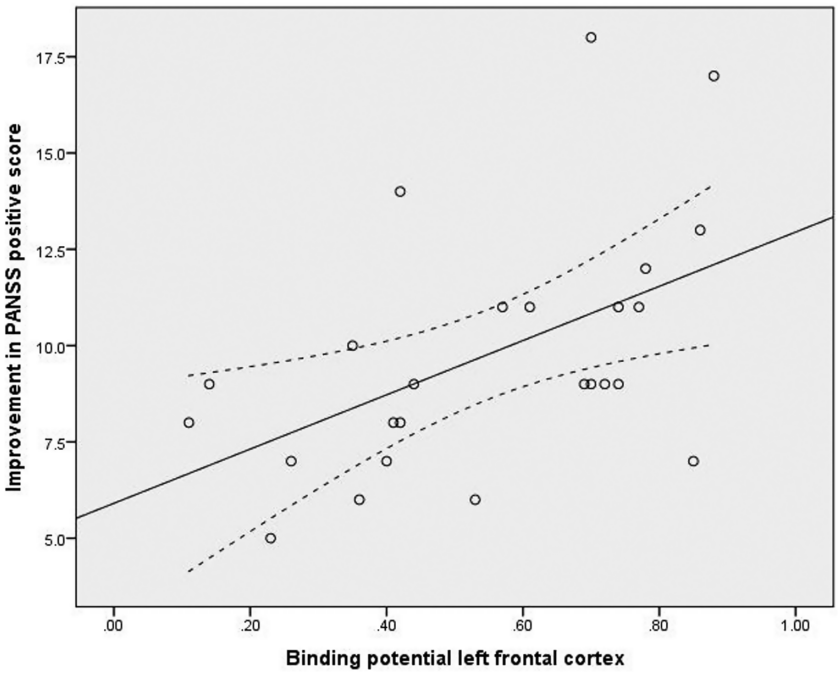

Figure 2. Correlation between left frontal dopamine $D_{2/3}$ receptor binding potential (BP_{ND}) in the antipsychotic-naïve state and treatment outcome. Improvement in Positive and Negative Syndrome Scale (PANSS) positive score (follow-up minus baseline) after 3 months of treatment: n = 25, rho = 0.56, $P < 0.01$. Linear regression shown as fully drawn line and confidence intervals as dashed lines.

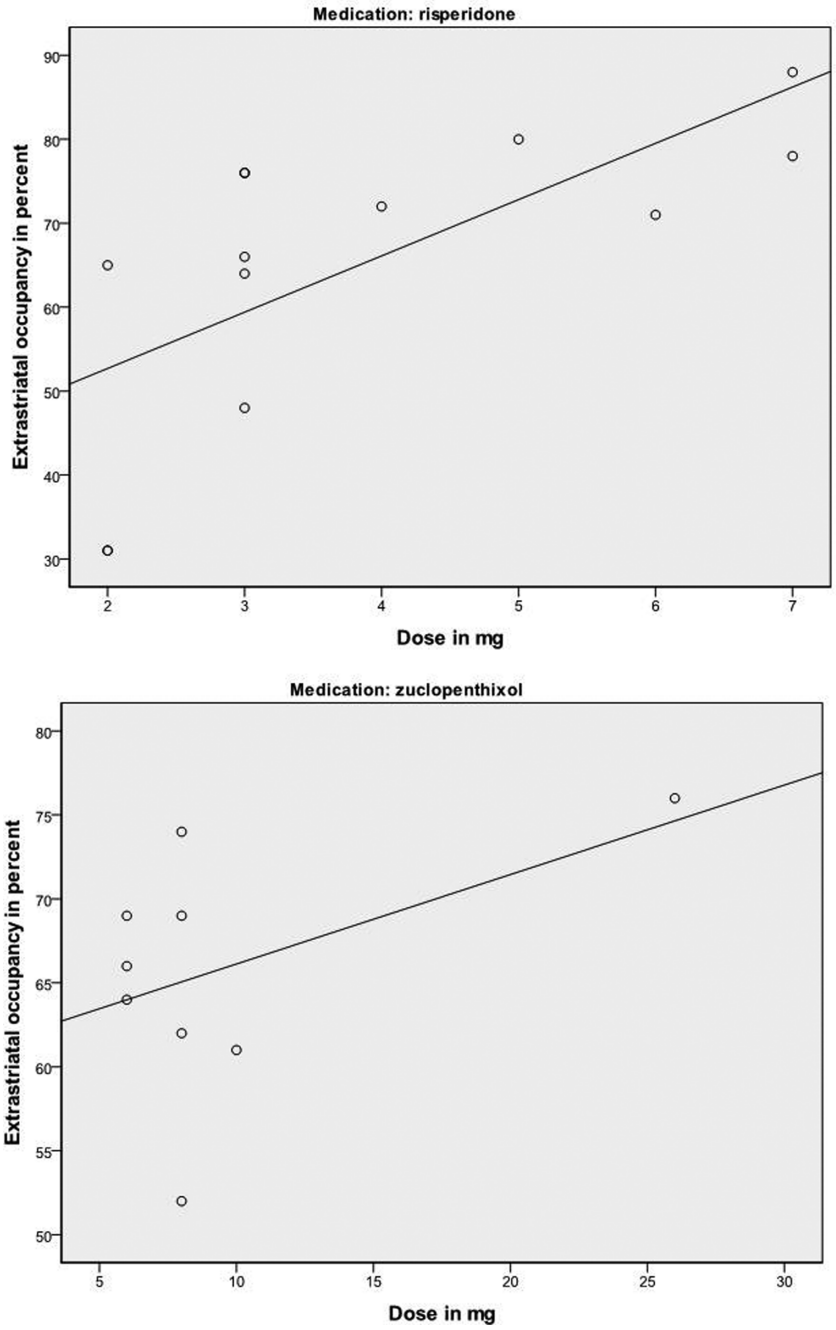

Figure 3. (A-B) Scatter plots showing correlations between dose and extrastriatal dopamine $D_{2/3}$ receptor occupancy in the 2 treatment groups. Patients treated with risperidone had significant correlations between dose and occupancy (n = 13, r = 0.68, *P* = .01). For patients treated with zuclopenthixol, no significant correlations were found (n = 9, r = 0.46, *P* = .2).

possibly by overshooting the optimal window for cognitive processing, perhaps similar to the inverted U-curve involvement of frontal dopamine D_1 receptors' function in working memory (Brozoski et al., 1979; Williams and Goldman-Rakic, 1995; Arnsten, 2013). Although these cognitive domains did not worsen significantly from baseline to follow-up, the strength of the negative correlations between follow-up scores, especially on attention with occupancy, suggests that the impact of occupancy is not negligible. In the zuclopenthixol group, occupancy explained as much as 62% of the variance in attention at follow-up, indicating that attentional focus and selection may be more detrimentally affected by dopamine $D_{2/3}$ receptor blockade than any of the other functions (Fagerlund et al., 2013). This is in line with other previous studies (Harris et al., 2009; Sakurai et al., 2013; Keedy et al., 2014), which together indicate that frontal $D_{2/3}$ receptors appear to be involved in the selection of relevant information for processing (Seamans and Yang, 2004), while D_1 receptors are crucially involved in the maintenance of information, for example, in working memory (Goldman-Rakic, 1995). This is clinically relevant, because some of the cognitive deficits that are present at illness onset may be further compromised by high $D_{2/3}$ receptor blockade (Fervaha

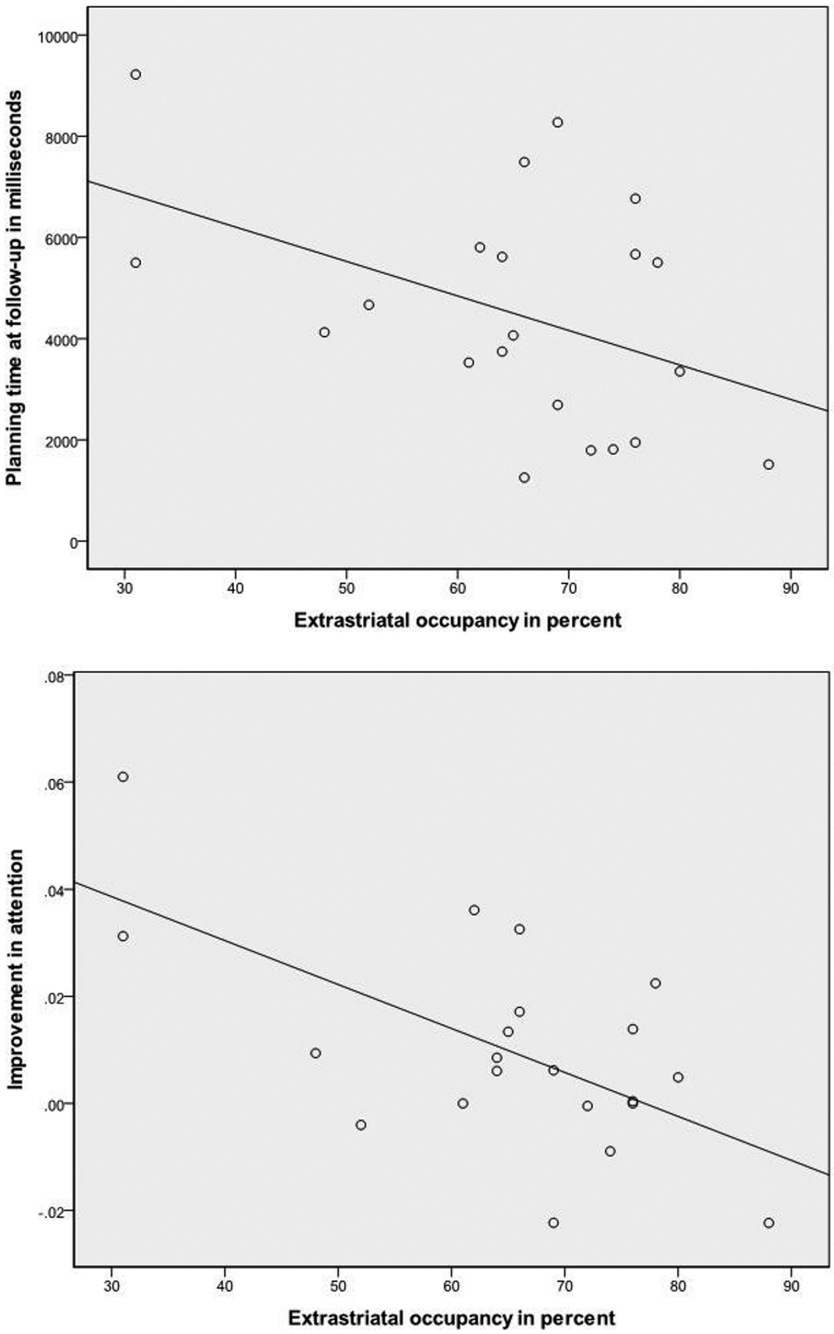

Figure 4. Scatter plots showing correlations between extrastriatal dopamine $D_{2/3}$ receptor occupancy and cognitive measures. (A) Planning time at follow-up measured with CANTAB (Stockings of Cambridge initial thinking time) (n = 21, r = -0.436, P = .048). Extrastriatal occupancy is in percent, planning time in msek. (B) Improvement in attention measured with CANTAB (signal detection measure A' from the Rapid Visual Information Processing test) (n = 21, r = -0.615, P = .003). Occupancy is in percent, and attention scores range from 0 to 1, with 1 indicating optimal signal detection.

et al., 2014; Lepage et al., 2014), which is also indicated by our present data.

Our data on baseline frontal $D_{2/3}$ receptor BP_{ND} and improvement of positive symptoms support that high frontal $D_{2/3}$ receptor availability is associated with treatment response in antipsychotic-naïve first-episode schizophrenia patients. This was the case for the total group of patients as well as the group treated with risperidone. Since patients and controls did not differ significantly with regard to BP_{ND} at baseline (Glenthoj et al., 2006), it suggests a receptor-mediated effect which is in accordance with the model of Seamans and Yang (2004) and in line with the hypothesized dopamine D_2 receptor high-affinity state model (Seeman, 2013). Thus, frontal BP_{ND} may predict treatment response in antipsychotic-naïve patients before the patient's first treatment with a dopamine antagonist. We did not find significant correlations between $D_{2/3}$ receptor BP_{ND} and change in PANSS positive scores in the smaller group of patients treated with zuclopenthixol. This is likely due to the uniform dosing with most patients receiving 8 or 10 mg.

In apparent opposition to both the demonstrated connection between baseline $D_{2/3}$ receptor BP_{ND} values, positive symptoms (Glenthoj et al., 2006), treatment outcome, as well as the

previously described model by Seamans and Yang (2004), our data could not directly confirm an association between blockade of frontal $D_{2/3}$ receptors and treatment effect on positive symptoms. A likely contributory factor to the seemingly conflicting results could be interactions between frontal and subcortical dopamine activity (Wilkinson, 1997; Clarke et al., 2014). Blockade of frontal $D_{2/3}$ receptors is believed to cause an increase in dopamine release in the nucleus accumbens (Del and Mora, 2005), hereby opposing the effect of frontal blockade on positive psychotic symptoms. This is indirectly supported by a recent study on a different cohort from our group. In this study, low $D_{2/3}$ receptor BP_P in the caudate at baseline was significantly associated with effect of treatment on positive symptoms with the relatively selective dopamine $D_{2/3}$ receptor antagonist, amisulpride, in initially antipsychotic-naïve first-episode schizophrenia patients (Wulff et al., 2015). Moreover, data also pointed to a negative effect of $D_{2/3}$ receptor blockade on level of function, which is in agreement with the present findings of a negative association between occupancy and certain cognitive functions.

Strengths and Limitations

The inclusion of antipsychotic-naïve first-episode schizophrenia patients enables assessment of biochemical markers before confounding factors like medication and chronicity, and the longitudinal design is optimal for relating these biomarkers to changes in symptom domains over time. Before completion of all follow-up examinations, 3 patients dropped out, corresponding to a very low attrition rate of 12%. Apart from all being in the risperidone group, the dropouts did not differ with regard to clinical and neurochemical values. Treatment period and doses were also comparable with the other patients (Table 1) with a mean dose of 3.3 mg. Hence, we judge attrition bias unlikely to have affected our results.

Inherently, correlation analyses show only associations and not a causal relationship between BP_{ND} and improvement in PANSS scores and our analysis on PANSS scores are not corrected for multiple comparisons, which increase the risk for type one errors, though we did have strong a priori hypotheses supporting the findings. As in the previous papers based on the same cohort of patients, we used the change measures in the PANSS positive score (calculated by subtraction of the 2 scores) to assess the effect of blockade on positive symptoms. This allows us to compare the present with previous data on the same patients. We have not included remission as an outcome measure, since our hypothesis was related to the change in the PANSS positive score. Even so, other factors like endogenous dopamine and other transmitter systems, for example, serotonin 2A receptors (Rasmussen et al., 2010, 2011; Ebdrup et al., 2011), may be involved in psychosis and affect our results.

We found that extrastriatal occupancy affected aspects of cognition. It is, however, important to keep in mind that extrastriatal occupancy is a global measure of cortical dopamine $D_{2/3}$ receptor blockade, and we cannot separate frontal from temporal blockade in this study. Thus, we cannot exclude that direct blockade of temporal $D_{2/3}$ receptors or interactions with temporal $D_{2/3}$ receptors may also have affected cognition (Tregellas et al., 2014). Regarding cognition, our results would not have survived Bonferroni correction, but because we had a strong a priori hypothesis regarding the relation between dopamine blockade and change in cognition (Fagerlund et al., 2004, 2013), we did not correct for multiple comparisons.

Furthermore, the size of the ROIs hampers a more detailed analysis of the BP_{ND} of specific subregions, for example, dorsolateral prefrontal cortex (Figure 1). Finally, the affinity of epidepride makes it impossible to distinguish between D_2- and D_3 receptors, but we note that D_3 receptors are sparsely represented in cortex (Beaulieu and Gainetdinov, 2011).

Conclusion

Taken together with our previous baseline data (Glenthøj et al. 2006; Fagerlund et al., 2013), the present results support that frontal dopamine $D_{2/3}$ receptors are involved in psychopathological and some cognitive processes in antipsychotic-naïve first-episode schizophrenia patients. The data did not point to an association between high frontal occupancy and treatment effect. On the contrary, they support that blockade of frontal $D_{2/3}$ receptors by antipsychotics may worsen some cognitive domains possibly by compromising the optimal prefrontal network functioning, which is required for cognitive performance, motivation, and learning. This is highly clinically relevant given the association between cognitive performance and functional outcome. In addition, the data showed an association between higher extrastriatal baseline BP_{ND} in antipsychotic-naïve patients and the effect of their first antipsychotic treatment on positive symptoms. This further supports the hypothesis of a differentiated treatment outcome of antipsychotic treatment based on the patient's dopamine activity at baseline.

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Statement of Interest

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