Psychopharmacology (2018) 235:2221–2232
https://doi.org/10.1007/s00213-018-4916-6

ORIGINAL INVESTIGATION

The role of striatal dopamine $D_{2/3}$ receptors in cognitive performance in drug-free patients with schizophrenia

Tanja Veselinović[1,2] · Ingo Vernaleken[1,2] · Hildegard Janouschek[3,4] · Paul Cumming[5] · Michael Paulzen[1,2,6] · Felix M. Mottaghy[7,8] · Gerhard Gründer[9]

Received: 10 August 2017 / Accepted: 18 April 2018 / Published online: 1 May 2018

Abstract

Objective A considerable body of research links cognitive function to dopaminergic transmission in the prefrontal cortex, but less is known about cognition in relation to striatal dopamine $D_{2/3}$ receptors in unmedicated patients with psychosis.

Methods We investigated this association by obtaining PET recordings with the high-affinity $D_{2/3}$ antagonist ligand [^{18}F] fallypride in 15 medication-free patients with schizophrenia and 11 healthy controls. On the day of PET scanning, we undertook comprehensive neuropsychological testing and assessment of psychopathology using the Positive and Negative Syndrome Scale (PANSS).

Results The patients' performance in cognitive tests was significantly impaired in almost all domains. Irrespective of medication history, the mean [^{18}F] fallypride binding potential (BP_{ND}) in the patient group tended to be globally 5–10% higher than that of the control group, but without reaching significance in any brain region. There were significant positive correlations between individual patient performance in the Trail Making Test (TMT(A) and TMT(B)) and Digit-Symbol-Substitution-Test with regional [^{18}F] fallypride BP_{ND}, which remained significant after Bonferroni correction for the TMT(A) in caudate nucleus (CN) and for the TMT(B) in CN and putamen. No such correlations were evident in the control group.

Discussion The association between better cognitive performance and greater BP_{ND} in schizophrenia patients may imply that relatively lower receptor occupancy by endogenous dopamine favors better sparing of cognitive function. Absence of comparable correlations in healthy controls could indicate a greater involvement of signaling at dopamine $D_{2/3}$ receptors in certain cognitive functions in schizophrenia patients than in healthy controls.

Keywords Cognitive impairments · Schizophrenia · Striatum · Dopamine $D_{2/3}$ receptors

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00213-018-4916-6) contains supplementary material, which is available to authorized users.

✉ Tanja Veselinović
tveselinovic@ukaachen.de

[1] Department of Psychiatry, Psychotherapy and Psychosomatics, Medical Faculty, RWTH Aachen University, Pauwelsstr. 30, 52074 Aachen, Germany

[2] Jülich Aachen Research Alliance JARA, Translational Brain Medicine, Jülich, Germany

[3] Department of Psychiatry and Iowa Neuroscience Institute, Roy J and Lucille A Carver College of Medicine, University of Iowa, Iowa City, IA, USA

[4] Department of Neurology, Medical Faculty, RWTH Aachen University, Aachen, Germany

[5] School of Psychology and Counselling and IHBI, Queensland University of Technology, and QIMR-Berghofer Institute, Brisbane, Australia

[6] Alexianer Hospital Aachen, Aachen, Germany

[7] Department of Nuclear Medicine, Medical Faculty, RWTH Aachen University, Aachen, Germany

[8] Department of Radiology and Nuclear Medicine, Maastricht University Medical Center (MUMC+), Maastricht, The Netherlands

[9] Department of Molecular Neuroimaging, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

Introduction

Impairments in a wide range of cognitive domains are coming to be recognized to constitute a core feature of schizophrenia (Green et al. 2004; Keefe et al. 2007). Indeed, impairments of memory and executive function are present in nearly all patients with schizophrenia (Keefe and Harvey 2012). While antipsychotic medications can relieve the positive symptoms of schizophrenia, cognitive impairments are often refractory to available treatments (Gray and Roth 2007). This appears to be of particular clinical importance, since the severity of cognitive impairments in schizophrenia is a better predictor of poor functional outcome than are indices from any other psychopathology domain (Green and Harvey 2014). Ref. "Green et al. 2004" is cited in the body but its bibliographic information is missing. Kindly provide its bibliographic information in the list.Green MF, Nuechterlein KH, Gold JM, Barch DM, Cohen J, Essock S, Fenton WS, Frese F, Goldberg TE, Heaton RK, Keefe RS, Kern RS, Kraemer H, Stover E, Weinberger DR, Zalcman S, Marder SR (2004) Approaching a consensus cognitive battery for clinical trials in schizophrenia: the NIMH-MATRICS conference to select cognitive domains and test criteria. Biol Psychiatry 56(5):301-7

Investigations over the past decades link the cognitive impairments in schizophrenia to dysfunction of several neurotransmitter systems, including brain dopamine (Tamminga 2006). According to an influential model, cognitive impairments of schizophrenia arise in relation to a biphasic dysregulation of dopaminergic signaling, with overactivity of mesolimbic pathways and underactivity of mesocortical dopamine pathways (Buchanan et al. 2007). Recurrent loops connecting striatum with the prefrontal cortex are heavily modulated by dopaminergic neurotransmission (Carter et al. 2001; Helmich et al. 2010; Robinson et al. 2012). While there are well-established findings of a relationship between D_1-mediated dopaminergic hypofunction in the prefrontal cortex with perturbation of certain cognitive domains (Goldman-Rakic et al. 2000; Minzenberg et al. 2009; Takahashi 2013), less is known about specific contributions of dopamine $D_{2/3}$ receptor-mediated striatal neurotransmission in cognitive impairments in schizophrenia.

Results of several molecular imaging investigations by positron emission tomography (PET) in healthy volunteers show associations between cognition and dopaminergic neurotransmission in striatum. Thus, Volkow and colleagues showed a robust positive correlation between neurocognitive test performance and striatal $D_{2/3}$ receptor availability (measured by [^{11}C]raclopride-PET) in a group of 30 healthy volunteers, which remained significant after controlling for age effects (Volkow et al. 1998). In another PET study of 11 healthy participants, Backman et al. reported that higher $D_{2/3}$ availability (measured as higher (in vivo) dopamine receptor binding potentials (BP_{ND})) was a better predictor for cognitive performance than was age (Backman et al. 2000). Furthermore, higher $D_{2/3}$ binding in the left caudate nucleus (CN) and putamen in a group of 30 healthy post-menopausal women predicted better executive function, indicated by performance of the Tower of London test of spatial planning (Reeves et al. 2005). Two other groups reported significant positive correlations between the performance in several cognitive tasks for executive functions and the striatal $D_{2/3}$ receptor availability measured with [^{11}C]raclopride-PET (Lawrence et al. 1998; Pavese et al. 2003). More recently, [^{11}C]raclopride binding in CN proved to correlate with scores in a test of episodic memory of a large series of healthy elderly adults (Nyberg et al. 2016). Thus, there is a general relationship between striatal dopamine $D_{2/3}$ receptor availability and executive function in healthy subjects across a wide range of ages.

In contrast to these findings in healthy volunteers, a consistent relationship between striatal dopaminergic markers and cognitive dysfunctions typically seen in schizophrenia is less clearly established. Meta-analysis of many molecular imaging studies reveals a hyperdopaminergic state in the striatum of patients with schizophrenia (Howes et al. 2012). Further, striatal dysfunction underlies particular aspects of perturbed cognition in schizophrenia (Simpson et al. 2010). One study showed a significant negative correlation between striatal dopamine transporter availability and cognitive symptoms, as measured by the PANSS cognitive component, in a group of ten schizophrenia patients (Yoder et al. 2004). In a single photon emission-computed tomography (SPECT) study of striatal dopamine $D_{2/3}$ receptors, striatal binding in schizophrenia patients correlated with fine motor function and with performance in attentional tests (Yang et al. 2004a). However, these investigations were all performed in patients with uninterrupted antipsychotic medication. To avoid the confounding effects of recent use of antipsychotic medications, we undertook an [^{18}F]fallypride PET study of dopamine $D_{2/3}$ receptors in a group of healthy volunteers and in patients who had been either drug-naïve or medication-free for at least 6 months prior to scanning. We used [^{18}F]fallypride as a tracer due to its high $D_{2/3}$ receptor affinity, long physical half-life (109 min), and suitability for the quantification of striatal and extra-striatal $D_{2/3}$ receptors during a single PET session (Mukherjee et al. 1995; Vernaleken et al. 2011). We then undertook an exploratory investigation of relationships between individual cognitive function and PET findings in the patient and control groups, testing the hypothesis that greater $D_{2/3}$ receptor availability in striatum correlates with better performance in tests of executive function in healthy controls, and likewise in unmedicated patients with schizophrenia.

Methods

This study was approved by all responsible authorities: The Federal Institute for Pharmaceuticals and Medical Products (Bundesamt für Arzneimittel (BfArM), Bonn), the local ethics committee of the Medical Faculty of the RWTH Aachen University (Aachen, Germany), and the German national

radiation safety authorities (Bundesamt für Strahlenschutz (BfS)). The examination procedure was explained in detail to all subjects, who afterwards signed a written informed consent. All investigations were performed in the Department of Psychiatry, Psychotherapy and Psychosomatics and the Department of Nuclear Medicine of the RWTH Aachen University, Germany.

Subjects

The patient group consisted of 15 patients with schizophrenia (ten males and five females of mean age 30.2 years (SD 10.9; range 18–52 years), being medication-free for at least 6 months prior to PET scanning ($N = 9$) or drug-naïve ($N = 6$). The mean duration of illness was 2 years (SD 5; range 0.5 to 7 years). The six drug-naïve patients were diagnosed with a first episode of schizophrenia (mean duration of symptoms: 6 to 9 months). A group of 11 healthy volunteers (seven males and four females) of mean age 30.6 years (SD 9.6; range 19–48 years) matched for level of education served as a control group.

Inclusion criteria consisted of normal findings in standard laboratory parameters (small blood count, coagulation factors, electrolytes, liver values, creatine kinase and TSH), electrocardiogram and electroencephalogram, as well as negative urine screening for illegal drugs (amphetamines, barbiturates, cocaine, marijuana, opiates, and methadone using a standard pharmacy test) at interview and on the day of PET scanning. For females, a negative pregnancy test and reliable contraception was required, along with a confirmatory negative pregnancy test on the day of PET scanning. A further prerequisite for inclusion was provision of freely given, signed informed consent. In the case of patients, physicians not involved in the study had vetted the participants' capacity to give informed consent. Prior to inclusion, all subjects were carefully examined for presence of any exclusion criterion (any relevant DSM-IV axis I disease other than schizophrenia or schizoaffective disorder, current use of psychotropic drugs of abuse, or any other relevant past or present serious medical or neurological diseases).

All subjects received a small compensation for their participation in the form of vouchers to a value of 100 Euros. This research was conducted in strict accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its most recent revision. Detailed demographic and psychopathological data of the included subjects are given in Table 1.

Study design

The neurocognitive assessment and the clinical examination took place on the same day as the [^{18}F]fallypride PET scan. In order to evaluate some cognitive domains known to be impaired in schizophrenia (Nuechterlein et al. 2008), the following four tests were administered to all subject:

(1) Trail-Making Test (TMT(A/B)) (Reitan 1958), a widely used test of high sensitivity, but somewhat low specificity (Kortte et al. 2002), which consists of two parts. In part A, the participant is instructed to draw a line connecting 25 numbers consecutively as quickly as possible. In part B, the participant alternates between consecutive numbers and letters. Performance of A and B is

Table 1 Demographic and psychopathological data of patients with schizophrenia and healthy control subjects

Parameter	Patients			Controls ($N = 11$)	Patients vs. controls (p*)
	All ($N = 15$)	Drug-naive ($N = 6$)	Previously medicated ($N = 9$)		
Age	29.8 (9.2)	27.8 (11.3)	29.4 (8.2)	30.6 (9.6)	0.621
Education years	11.8 (1.3)	12.8 (0.4)	11.1 (1.3)	12.5 (1.7)	0.217
Gender (M/F)	10/5	4/2	6/3	7/4	0.598
Handiness (number right/left-handed)	13/2	5/1	8/1	9/2	0.468
Smoking status (non-smoker/smoker)	10/5	4/2	6/3	8/3	0.543
Duration of illness (Years)	2.1 (5.1)	0.7 (0.4)	4.1 (6.4)	–	
PANSS total score mean	79.2 (9.2)	79 (9.2)	81.6 (13.3)	–	
PANSS positive	23.1 (5.2)	24.8 (5.8)	21.8 (4.8)	–	
PANSS negative	19.7 (7.5)	15.3 (2.6)	22.6 (8.5)	–	
PANSS general	37.9 (5.6)	38.8 (3.3)	37.2 (6.8)	–	
Primary diagnosis, DSM-IV (no. by diagnosis)					
Schizophrenia, paranoid type	12	5	7	–	
Schizophrenia, undifferentiated type	1	1	0	–	
Schizoaffective disorder	2	0	2	–	

For age, education years, illness duration, and the PANSS scores, values are given as mean (SD)

*For p value calculation, we used the Mann-Whitney test for age and education years and the chi-quadrat test for gender, handiness, and smoking status

scored as the time taken to complete each trial without error. The TMT(A/B) reflects a combination of several cognitive functions, measuring complex visual scanning with a motor component, motor speed, and agility. Part B, which entails a greater cognitive burden, is particularly sensitive to deficits in cognitive flexibility and executive function (Kortte et al. 2002).

(2) Digit-Symbol-Substitution Task (DSST) a subtest of the Wechsler Intelligence Scale (Wechsler 1997) primarily quantifies the speed of mental processing. Participants are instructed to pair symbols to numbers and write them into blank squares as quickly as possible, while referring to a digit-symbol key presented at the top of the examination sheet. The DSST score is the number of correct substitutions made in 90 s.

(3) Verbal Fluency Task ("Regensburger Wortfluessigkeitstest"; RWT) (Harth et al. 2004) is a verbal fluency test standardized for German language. The test consists of four parts, designed to assess phonemic and semantic fluency and the ability for category change. The observation time for each part is 1 min.

(4) Letter-Number Span (Gold et al. 1997) a test of working memory performance in which the examiner presents a series of increasingly longer sequences of intermixed numbers and letters (2 to 7 stimuli) at a rate of 1/s. After each sequence presentation, the participant is asked to first repeat the numbers in ascending order and then the letters in alphabetical order. Four trials are presented for each sequence length; the test is concluded when the subject fails four consecutive trials of the same length. One point is scored for each correctly repeated sequence, to a maximum of 24 points.

Radiochemistry and data acquisition

The radiosynthesis of [^{18}F]fallypride, as described in detail earlier (Vernaleken et al. 2013), is obtained by a high-yield modification of the synthesis method for [^{18}F]desmethoxyfallypride (Gründer et al. 2003). A high-resolution Siemens ECAT EXACT 922/47 whole-body PET scanner (Siemens AG, Germany) was used to acquire dynamic emission images in 3D-mode (field-of-view 16.2 cm; 47 planes; full width a half maximum (FWHM) axial 4.6 mm, in-plane: 6.0 mm). The standard procedure for the dynamic data acquisition comprised 39 sequential time frames (3 × 20 s, 3 × 1 min, 3 × 2 min, 3 × 3 min, 21 × 5 min, 2 × 8 min, 4 × 10 min) to a total of 180 min. A 15-min transmission scan using a ^{68}Ge source performed prior to tracer administration enabled the subsequent attenuation correction of the emission sequence. A vacuum mask was used for comfortable immobilization of the subject's head during the scanning procedure. We applied fiducial felt-tip marks to the head to monitor for excessive head displacement between the transmission scan and the tracer administration. A mean of 213 ± 30 MBq [^{18}F]fallypride was injected as a slow bolus to the cubital vein in the non-dominant arm (patients 214 ± 31 MBq, controls: 213 ± 30 MBq; $p = 0.967$ paired t test). The specific activity was 1483 ± 1350 (range 131–5022) GBq/μmol (patients 1471 ± 1574 GBq/μmol; controls 1495 ± 1420 GBq/μmol; $p = 0.89$; paired t test), corresponding in each case to < 1 nmol mass injected. The injected mass did not significantly correlate with the measured BP_{ND} in any region, neither in patients nor in healthy volunteers.

Image and data analysis

We applied a Hanning filter (4 mm FWHM) and filtered back-projection for the reconstruction of emission frames. We then applied a nonlinear spatial normalization of the summed dynamic baseline scan to a template in the MNI space using the MEDx software (v3.43; Medical Numerics, USA) with six parameters after a frame-by-frame motion-correction. Next, we applied anatomic templates as polygonal volumes of interest (VOIs) for extraction of time-activity curves (TACs) from cerebellum, and bilateral putamen (PUT), caudate nucleus (CN), thalamus (THAL), and inferior temporal gyrus (ITG). These VOIs are representative of the main brain regions with reliably quantifiable [^{18}F]fallypride binding and have been used in several of our previous investigations (e.g., (Gründer et al. 2008; Vernaleken et al. 2010, 2013)). The [^{18}F]fallypride binding potentials (BP_{ND}) of the VOIs were calculated using the simplified reference tissue model (SRTM), with cerebellum serving as the reference region (Lammertsma and Hume 1996). While there are traces of $D_{2/3}$ receptor binding in cerebellum (0.13% of putamen binding; (Hall et al. 1996)), its use as a reference region for calculating [^{18}F]fallypride BP_{ND} in our VOIs is a widely established approach (Siessmeier et al. 2005; Vernaleken et al. 2011; Ishibashi et al. 2013; Cumming et al. 2013). We cannot completely exclude the possibility that our BP_{ND} values were slightly underestimated because of traces of specific binding in the cerebellum. However, the low magnitude of this binding (Langer et al. 2017) predicts low bias in striatum, albeit with relatively higher bias in the cerebral cortex, where specific binding is also low. Further, the strong correlation (correlation coefficient greater than 0.99 with a slope of 1.0) between regional BP_{ND}s obtained with the STRM and BP_{ND}s obtained with metabolite-corrected plasma input function (Kessler et al. 2005) also suggests that the bias should be consistently less than 5% for our reference tissue method (Olsson et al. 2004; Gründer et al. 2008). All participants were under medical supervision during the PET recording and afterwards for at least an additional 2 h. None of the included subjects dropped out or experienced any noteworthy adverse events during the PET examination.

Statistical analysis

We used the SPSS statistical analysis software package (SPSS Version 20 for Windows; IBM, New York, NY, USA) for all analyses. The BP_{ND}-values calculated in the VOIs and scores from the neuropsychological tests were compared between the groups using a non-parametric Mann-Whitney test, in keeping with the small sample size. Effect sizes (ES) were calculated for each comparison using the open source software G*Power (Faul et al. 2007). In the next step, we carried out an exploratory regression analysis testing for group-wise relationships between regional [^{18}F]fallypride BP_{ND} and cognitive test scores. Due to heteroscedasticity of most of the measured parameters, we used the Spearman rank-order correlation. The significance level was set to 0.05. Bonferroni correction was applied to accommodate problems due to multiple testing.

Results

$D_{2/3}$ receptor availability

Mean BP_{ND}-values measured in the VOIs for the patient and control groups are presented in Table 2; coefficients of variation were less than 27% in all four brain regions considered. Receptor availability was 5–10% higher in the patient group for all VOIs examined, but without reaching statistical significance. In Table 2, we separately depict mean BP_{ND}-values measured in the two patient subgroups according to disease stage (six de novo, drug-naïve patients and nine previously medicated patients, drug-free for at least 6 months at the time of scanning). The mean BP_{ND}-values did not differ between subgroups in any of the four regions ($p < 0.05$ for all regions; no Bonferroni correction).

There were no significant correlations between regional BP_{ND} and age (patients: ITG $r = -0.27$, $p = 0.33$; THAL $r = 0.36$, $p = 0.19$; CN $r = -0.43$, $p = 0.11$; PUT $r = -0.46$, $p = 0.1$; controls: ITG $r = 0.14$, $p = 0.68$; THAL $r = 0.27$, $p = 0.42$; CN $r = -0.29$; $p = 0.4$; PUT $r = -0.09$, $p = 0.79$), nor were there any associations with illness duration in the patient group (ITG $r = -0.21$, $p = 0.46$; THAL $r = 0.05$, $p = 0.87$; CN $r = -0.19$, $p = 0.50$; PUT $r = 0.02$, $p = 0.94$).

Cognitive performance

Patients performed worse than controls in almost all neuropsychological tests (Table 3). Even after Bonferroni correction (for a total of eight subtests of four tests), the results in the patient group were significantly worse for the following tests: (1) TMT–TMT(A); 38.3 ± 12.6 s (patients) versus 25.1 ± 7.7 s (controls; $p = 0.003$); (2) TMT(B); 87.1 ± 27.3 s (patients) versus 56.5 ± 19.3 s (controls; $p = 0.005$); (3) DSST; 42.7 ± 10.9 (patients) versus 60.6 ± 14.7 (controls; $p = 0.003$); and (4) the verbal-fluency task for phonemic fluency; 8.1 ± 3.8 (patients) versus 13.2 ± 3.8 (controls; $p = 0.003$), semantic fluency; 16.3 ± 6.3 (patients) versus 23.7 ± 4.8 (controls; $p = 0.002$) and semantic category change; 11.5 ± 3.8 (patients) versus 16.7 ± 3.7 (controls; $p = 0.002$). We saw no evidence for differences

Table 2 Results by volume of interest (VOI) analysis of dopamine $D_{2/3}$ receptor availability (BP_{ND}) to [^{18}F]fallypride PET in groups of unmedicated patients with schizophrenia ($N = 15$) and healthy controls ($N = 11$)

VOI	Patients				Controls		Patients vs. controls		
	All ($N = 15$)		Drug-naive ($N = 6$)	Previously medicated ($N = 9$)					
	BP_{ND} (SD)	CV (%)	BP_{ND} (SD)	BP_{ND} (SD)	BP_{ND} (SD)	CV (%)	% difference	Mann-Whitney test (p)	Effect size
ITG	0.75 (0.20)	26.7	0.71 (0.08)	0.78 (0.3)	0.7 (0.21)	29.2	7%	0.44	0.25
THAL (left)	1.99 (0.46)	23.2	2.05 (0.3)	1.95 (0.6)	1.91 (0.50)	26.4	9%	0.61	0.17
THAL (right)	2.01 (0.46)	22.9	2.07 (0.3)	1.96 (0.5)	1.94 (0.47)	24.3	4%	0.30	0.15
THAL (mean)	2 (0.45)	22.7	2.06 (0.3)	1.96 (0.6)	1.93 (0.47)	24.4	4%	0.47	0.15
CN (left)	19.9 (4.0)	20.2	21.6 (2.8)	18.8 (4.4)	18.6 (3.3)	17.9	7%	0.41	0.32
CN (right)	20.5 (4.5)	21.8	21.9 (3.6)	19.4 (4.8)	18.6 (3.1)	16.5	10%	0.24	0.43
CN (mean)	20.2 (4.2)	20.8	21.8 (3.2)	19.1 (4.6)	18.6 (3.2)	16.9	9%	0.26	0.43
PUT (left)	21.9 (4.6)	20.9	23.5 (3.4)	20.9 (5.2)	20.2 (3.8)	18.8	9%	0.20	0.39
PUT (right)	22.0 (4.9)	22.2	23.8 (3.9)	20.9 (5.3)	20.0 (3.7)	18.4	10%	0.24	0.46
PUT (mean)	22.0 (4.7)	21.3	23.6 (3.6)	20.9 (5.2)	20.1 (3.7)	18.4	10%	0.20	0.45

Statistical results are presented in the right-hand columns. Results are also reported for medication-free and never-medicated subgroups of schizophrenia patients. Bonferroni's correction: adjusted significance level after correcting for four regions: $p < 0.0125$

ITG inferior temporal gyrus, *THAL* thalamus, *CN* caudate nucleus, *PUT* putamen. *CV* coefficient of variation (calculated as: (SD/mean)*100). *% difference* percentage difference (calculated as the patient result relative to the control group)

Table 3 Results of the paper/pencil tests in groups of ($N = 15$) patients with schizophrenia and ($N = 11$) healthy controls. Test scores in each group are presented as the group mean (SD)

Task	Patients			Controls	Patients vs. controls	
	All ($N = 15$)	Drug-naive ($N = 6$)	Previously medicated ($N = 9$)		Mann-Whitney test (p)	Effect size
TMT (A)	38.3 (12.6)	36.9 (14.7)	39.2 (11.9)	25.1 (7.7)	0.002**	1.06
TMT (B)	87.1 (27.3)	75.5 (16.2)	94.7 (39.8)	56.5 (19.3)	0.003**	0.96
LNS	13.1 (3.5)	15 (2)	12.8 (3.8)	16.7 (3.1)	0.013*	0.94
DSST	42.7 (10.9)	50.3 (8.1)	42.7 (9.7)	60.6 (14.7)	0.001**	1.17
RWT-phonemic fluency	8.1 (3.8)	10 (2.3)	7.7 (4.1)	13.2 (3.8)	0.002**	1.12
RWT-semantic fluency	16. 3 (6.3)	18.5 (7.9)	15.9 (4.9)	23.7 (4.8)	0.005**	1.1
RWT-phonemic cath. change	9.7 (5.1)	12.5 (6.8)	8.9 (2.6)	13.8 (5.2)	0.047*	0.74
RWT-semantic cath. change	11.5 (3.8)	11.8 (4.6)	11.3 (3.4)	16.7 (3.7)	0.003**	1.15

Mean results are also for medication free and never-medicated subgroups of schizophrenia patients

TMT Trail Making Test A and B (TMT(A/B)), *LNS* letter-number span, *DSST* digit-symbol-substitution task, *RWT* verbal fluency task ("Regensburger Wortfluessigkeitstest")

*Statistically significant differences: $p < 0.05$; **statistically significant differences surviving Bonferroni's correction (adjusted level for in total 8 subtests of 4 tests: $p < 0.006$)

in cognitive performance between the medication-naïve and previously medicated subgroups (Table 3).

Further, we observed in the patient group significant negative correlations between the times needed to perform the TMT(A) and TMT(B) tasks and the regional [^{18}F]fallypride BP_{ND}, irrespective of medication history (Table 4). These correlations were particularly strong in the bilateral CN (for TMT(A): left CN $r = -0.83$, $p < 0.001$; right NC $r = -0.86$, $p < 0.001$; for TMT(B): left CN $r = -0.81$, $p < 0.001$; right CN $r = -0.85$, $p < 0.001$) and in bilateral putamen (for TMT(A): left putamen: $r = -0.84$, $p < 0.001$, right putamen: $r = -0.81$, $p < 0.001$; for TMT(B): left putamen: $r = -0.85$, $p < 0.001$; right putamen $r = -0.83$, $p < 0.001$), remaining significant also after Bonferroni correction. Conversely, the DSST scores correlated positively with the [^{18}F]fallypride BP_{ND} in bilateral CN (left CN $r = 0.62$, $p = 0.014$; right CN $r = 0.57$; $p = 0.028$) and at trend-level in bilateral putamen (left putamen $r = 0.51$, $p = 0.056$; right putamen $r = 0.47$; $p = 0.079$), but these associations were not strong enough to survive Bonferroni correction. TMT(B) scores in the patients correlated significant with [^{18}F]fallypride BP_{ND} in the ITG ($r = -0.75$; $p = 0.001$), but not in THAL ($r = -0.44$, $p = 0.1$). There were no significant correlations between cognitive test scores and regional [^{18}F]fallypride BP_{ND} in the control group.

Discussion

This exploratory PET study aimed to contribute to a better understanding of the role of striatal dopaminergic neurotransmission in the cognitive impairments in schizophrenia. In previous molecular imaging studies, such relationships have emerged in healthy volunteers, but corresponding findings in schizophrenia patients are equivocal, and likely to have been confounded by medication. Thus, we tested for associations between cognitive performance and the $D_{2/3}$ receptor availability in striatum and in selected extrastriatal regions using the highly affine radioligand [^{18}F]fallypride, in groups of 15 schizophrenia patients (of whom six were medication naïve and nine had been medication free for at least 6 months) and in 11 demographically matched healthy volunteers.

Our study revealed two main findings: First, we observed a very strong association between performance in a test of executive function (TMT) and the $D_{2/3}$ receptor availability in striatum (CN and putamen), and the ITG cortex (but not THAL), irrespective of medication history in the schizophrenia patients. Second, we did not find corresponding relationships in the healthy control group, in whom $D_{2/3}$ receptor availability globally (but not statistically significantly) tended to be 5–10% lower.

Direct correlations between executive functions and the dopamine $D_{2/3}$ receptor availability in CN and putamen have been reported previously in healthy controls (Volkow et al. 1998; Backman et al. 2000; Reeves et al. 2005), but have not hitherto been investigated in medication-free schizophrenia patients. In our study, higher $D_{2/3}$ receptor availability in striatum of the patient group was associated with better performance (shorter performance times) in TMT(A) and TMT(B). Thus, relatively high dopamine $D_{2/3}$ receptor availability especially in striatum mitigates against aspects of cognitive dysfunction in these patients with schizophrenia. In general, observations of dopamine $D_{2/3}$ receptor availability for benzamide radioligands such as [^{18}F]fallypride are formally ambiguous, as the measured BP_{ND} is reduced to some unknown extent by competition from endogenous dopamine (Morris et al. 2010). Insofar as higher $D_{2/3}$

Table 4 Rank order correlations (two-sided Spearman correlation) between the regional $D_{2/3}$ receptor availability measured by [^{18}F]fallypride (binding potential; BP_{ND}) and the scores reached in the neuropsychological tests depicted separately for the patient and the control group Please give the significance of the italicized entries in Table 4 in the form of a table note; otherwise, amend if necessary.In the current version the italic fonts was used in combination with * and ** labeling for significant p values and corresponding r-values. This is somewhar superfluous, so that all entries in rhe table should be writen in the standard font, without italicization.

		Patients				Controls			
		ITG	THAL	CN	PUT	ITG	THAL	CN	PUT
TMT(A)	r_s	− .25	− .32	− .78**	− .65*	.08	.07	− .19	− .1
	p	.37	.24	.001**	.008*	.8	.83	.57	.77
	R^2	.06	.09	.61	.42	.006	.005	.04	.01
	BaC CI 95%	[− .8; .4]	[− .76; .34]	[− .99; − .24]	[− .99; .26]	[− .49; − .61]	[− .61; .73]	[− .93; .54]	[− .8; .63]
TMT(B)	r_s	− .75**	− .44	− .69**	− .74**	.22	.2	.03	.26
	p	.001**	.1	.004**	.002**	.51	.56	.93	.45
	R^2	.56	.19	.48	.54	.05	.04	.009	.07
	BaC CI 95%	[− .95; − .19]	[− .86; .26]	[− .93; − .11]	[− .96; − .19]	[− .49; .8]	[− .56; .9]	[− .8; .69]	[− .45; .83]
LNS	r_s	− .19	− .02	.04	− .01	− .31	− .46	− .43	− .48
	p	.51	.95	.89	.99	.35	.15	.09	.19
	R^2	.03	.0004	.002	.0001	.09	.2	.21	.23
	BaC CI 95%	[− .62; .34]	[− .51; .46]	[− .55; .61]	[− .56; .55]	[− .82; .87]	[− .9; .44]	[− .94; .13]	[− .94; .27]
DSST	r_s	.31	.22	.58*	.43	.34	.05	− .04	− .02
	p	.26	.44	.02*	.11	.29	.88	.9	.59
	R^2	.09	.05	.34	.18	.1	.003	.002	.0004
	BaC CI 95%	[− .33; .75]	[− .41; .69]	[.21; − 82]	[− .05; .73]	[− .38; .92]	[− .75; .8]	[− .78; .74]	[− .81; .61
RWT-phonemic fluency	r_s	.07	.03	.25	.32	− .37	− .26	− .42	− .28
	P	.81	.9	.38	.25	.26	.42	.19	.41
	R^2	.005	.0009	.06	.1	.14	.07	.18	.07
	BaC CI 95%	[− .49; .65]	[− .49; .61]	[− .21; .66]	[− .29; .81]	[− .92; .44]	[− .83; .65]	[− .97; .44]	[− .89; − .5]
RWT-semantic fluency	r_s	− .02	− .08	− .03	− .09	− .23	− .13	− .29	− .27
	p	.95	.77	.92	.76	.51	.71	.37	.43
	R^2	.0004	.006	.009	.008	.05	.02	.08	.07
	BaC CI 95%	[− .5; .44]	[− .59; .49]	[− .59; .55]	[− .56; .47]	[− .81; .56]	[− .79; .74]	[− .9; .57]	[− .88; .47]
RWT-phonemic cath. change	r_s	.15	.07	.43	.31	− .42	− .42	− .41	− .47
	p	.58	.79	.14	.28	.19	.18	.21	.14
	R^2	.02	.005	.18	.09	.18	.18	.17	.22
	BaC CI 95%	[− .35; .56]	[− .45; .66]	[− .09; .74]	[− .25; .71]	[− 86; .61]	[− .93; .31]	[− .95; .47]	[− .98; .32]
RWT-semantic cath. change	r_s	− .2	.12	− .05	− .24	.11	− .05	− .47	− .18
	p	.46	.67	.87	.39	.77	.89	.15	.59
	R^2	.04	.01	.003	.06	.01	.002	.22	.03
	BaC CI 95%	[− .63; .35]	[− .39;.6]	[− .67; .64]	[− .8; .32]	[− .63; .86]	[− .69; .71]	[− .91; .42]	[− .82; .67]

ITG inferior temporal gyrus, *THAL* thalamus, *CN* caudate nucleus, *PUT* putamen, *Ba CI 95%* 95% confidence interval with Bias-corrected accelerated bootstrapping

*Statistically significant correlations at the 0.05 level (twotailed); **statistically significant correlations surviving Bonferroni's correction (4 tests, 4 brain regions; adjusted sig. level $p < 0.006$)

availability favors cognitive performance in our patient group, this may imply that it is the dynamic range of dopamine signaling that determines cognitive flexibility. In this conjectural scenario, those patients with lower basal occupancy by endogenous dopamine in striatum, as indicated by relatively higher BP_{ND}, can accommodate a more robust dopaminergic response to a cognitive challenge. In support of this model, Rajji and colleagues reported a strong association between improving cognitive performance and increasing $D_{2/3}$ receptor availability in the whole striatum to [^{11}C]-raclopride PET in a geriatric sample followed after a dose reduction of antipsychotic medication (Rajji et al. 2017).

Further, in our patient group, the dopamine $D_{2/3}$ receptor availability in the cortical region ITG correlated with performance of the TMT(B) test. Due to its more complex design, the TMT(B) measures not only just visuomotor abilities, but also cognitive flexibility, set-shifting, and inhibition (Arbuthnott and Frank 2000; Kortte et al. 2002). Results of most functional neuroimaging studies emphasize the decisive role of the prefrontal cortex for the performance in TMT(B) (Allen et al. 2011), although some findings link TMT(B) scores directly with activation (Jacobson et al. 2011), perfusion (Horacek et al. 2006), and cortical thickness in the ITG (MacPherson et al. 2017). Furthermore, the ITG is implicated in several complex cognitive processes (Cabeza and Nyberg 2000), including visual perception (Ishai et al. 1999; Herath et al. 2001), which is a factor in TMT performance. However, it remains unclear whether our isolated finding speaks to the function of the ITG or rather sui generis for dopamine $D_{2/3}$ receptors in other cortical regions. In this regard, other molecular imaging results point to an association between $D_{2/3}$ availability in frontal regions and set shifting in antipsychotic-naïve, first episode schizophrenia patients (Fagerlund et al. 2013).

Surprisingly, we failed to detect correlations between cognitive performance and [^{18}F]fallypride BP_{ND} in our healthy control group. This could imply a certain robustness of cognition to individual differences in $D_{2/3}$ availability in healthy controls. Indeed, a moderate reduction of available $D_{2/3}$ receptors by a pharmacological blockade with sulpiride (17% occupancy to [^{11}C]raclopride-PET) was without effect on cognition of healthy volunteers, whereas a further receptor blockade (28% occupancy) induced some cognitive impairments (Mehta et al. 2008). Similar to our findings, another group reported a significant linear correlation between $D_{2/3}$ availability in frontal cortex and some cognitive domains in schizophrenia patients, but not in healthy controls (Fagerlund et al. 2013). One possible interpretation of such discrepancies could be that $D_{2/3}$ receptor availability has a greater impact on certain cognitive functions in schizophrenia patients than in healthy controls. Indeed, some previous investigations postulated that behavioral flexibility is supported by cooperative actions of D_1- and D_2-like receptors (Floresco and Magyar 2006), whereby $D_{2/3}$ receptor activation may mediate behavioral adjustment in novel situations, while concomitant D_1 receptor activation limits the cognitive focus and stabilizes the existing strategy (Seamans and Yang 2004; Floresco and Magyar 2006). Thus, the rigid association between some cognitive functions and $D_{2/3}$ receptor availability seen in our patients may translate to reduced behavioral and cognitive flexibility, which are among the most prevalent cognitive deficits associated with schizophrenia (Floresco et al. 2009).

In this study, we recapitulate our earlier findings of cognitive function deficits in un-medicated patients with schizophrenia (Veselinović et al. 2015). The generally poor cognitive performance in the patient group, particularly in the TMT, may be a marker for more general cognitive disorganization (Mahurin et al. 2006) or more specifically of impaired executive functions and cognitive flexibility (Kortte et al. 2002). Further, acute symptoms in our unmedicated sample may also have contributed to their worse cognitive performance in the TMT(B). In this task, positive symptoms could confound performance since visual scanning is involved, even as negative symptoms could impair the motor component. Indeed, numerous previous investigations speak on behalf of a moderate association between negative symptoms and neurocognition (Heydebrand et al. 2004; Ventura et al. 2009; Lindsberg et al. 2009; Leeson et al. 2010; Meyer et al. 2014) and a lesser association between positive symptoms and cognition (Addington et al. 2005; Ventura et al. 2009, 2010) in chronic and first-episode schizophrenia.

We found a trend towards globally 5–10% higher $D_{2/3}$ receptor availability in medication-free patients suffering from schizophrenia compared to age matched healthy volunteers. Previous studies report elevated $D_{2/3}$ receptor availability in comparable patients groups (Wong et al. 1986; Tune et al. 1993; Laruelle 1998; Kestler et al. 2001), or no significant difference (Hietala et al. 1994; Nordstrom et al. 1995; Yang et al. 2004b; Glenthoj et al. 2006; Suridjan et al. 2013). Howes and colleagues (Howes et al. 2012) confirmed in their comprehensive meta-analysis an increased $D_{2/3}$ receptor availability of small effect size in previously medicated patients with schizophrenia (Cohen $d = 0.26$, $p = 0.049$), as corroborated by two other meta-analyses of various SPECT and PET studies (Weinberger and Laruelle 2002; Brunelin et al. 2013). Mukherjee and colleagues reported a test–retest error for [^{18}F]fallypride BP_{ND} of up to 10% in a sample of six healthy normal subjects (Mukherjee et al. 2002), whereas other report rather good test-retest variability ranging from 4% in striatum to 6–8% in cortical regions (Cropley et al. 2008; Dunn et al. 2013). In any case, the present sample size is clearly inadequate to detect group differences in BP_{ND}, especially in consideration of the mixed treatment history; a simple power calculation suggests that a sample size of at least 64 per group would be required to detect a significant BP_{ND} difference assuming an effect size such as reported in the meta-analyses. The citation "Weinberger et al. 2002" has been changed to "Weinberger and Laruelle, 2002" to match the author name/date in the reference list. Please check if the change is fine in this occurrence and modify the subsequent occurrences, if necessary.I agree with the changed citation.

Sample size and test-retest stability are key issues in relation to the detection of small group differences in [^{18}F]fallypride BP_{ND}. Further limitations of our study are the relatively large age range of patients and controls, and the mixed patient group in relation to stage of illness/medication history. The wide age range arises from the logistics of recruitment of medication-free patients with schizophrenia. Nonetheless, we were unable to detect any age-dependence of BP_{ND}, either in the patient or control groups over an age

range of three decades, despite earlier reports of a > 10% decline in striatum with each decade of healthy aging (Bäckman et al. 2006; Cumming et al. 2013). This is likely due to inadequate power of the present study, which also failed to replicate a report of greater rate decline in $D_{2/3}$ receptor availability with increasing illness duration (Kestler et al. 2001). However, the present investigation was an exploratory and correlational study designed to search for associations between $D_{2/3}$ receptor availability and cognitive performance. As such, present findings should motivate further investigations in more narrowly defined groups.

Howes et al. attributed a slightly higher striatal $D_{2/3}$ availability in schizophrenia patients to persisting effects of recent exposure to antipsychotic medication (Howes et al. 2012). Six of our 15 patients had never been treated with an antipsychotic medication previously and had diagnosis of a first episode of schizophrenia, with symptom duration of 6 to 9 months, whereas the remaining nine patients had a longer duration of illness, and previous antipsychotic treatment. Although our sub-group sizes are too small to support comparisons, we suppose that this clinical heterogeneity may have contributed to dispersion of our molecular imaging results. In particular, previous history of antipsychotic medication may have altered dopamine receptor availability, as suggested by basic research showing that prolonged pharmacological blockade of $D_{2/3}$ dopamine receptors leads to a compensatory increase of their densities (Oda et al. 2015) or increased affinity state for dopamine agonists, i.e. sensitization (Seeman 2013).

In summary, we report a positive relationship between dopamine $D_{2,3}$ receptor availability in striatum and ITG with some aspects of cognition in a group of 15 schizophrenia patients, but no such relationships in healthy age-matched controls. This could indicate a greater involvement of signaling at dopamine $D_{2/3}$ receptors in certain cognitive functions in schizophrenia patients than in healthy controls. In this scenario, lower basal occupancy by endogenous dopamine in those patients with higher $D_{2,3}$ receptor availability may favor better cognitive performance and flexibility. Present results give heuristic support to the mechanism by which pharmacological blockade of dopamine $D_{2/3}$ receptors, intended to ameliorate positive symptoms of schizophrenia, may contribute to worsening of cognitive function and furthermore implicate neocortical as well as striatal receptors in these effects.

Funding information This study was supported by the German Research Association (Deutsche Forschungsgemeinschaft, DFG; KFO-112/2-1).

Compliance with ethical standards

Conflict of interest Dr. Vernaleken has served on the speakers' bureau of Bristol-Myers Squibb (New York, NY), Eli Lilly (Indianapolis, Ind), and GlaxoSmithKline (London, UK). Dr. Gründer has served as a consultant for Allergan (Dublin, Ireland), Boehringer Ingelheim (Ingelheim, Germany), Eli Lilly (Indianapolis, Ind, USA), Janssen-Cilag (Neuss, Germany), Lundbeck (Copenhagen, Denmark), Ono Pharmaceuticals (Osaka, Japan), Otsuka (Chiyoda, Japan), Recordati (Milan, Italy), Roche (Basel, Switzerland), Servier (Paris, France), and Takeda (Osaka, Japan). He has served on the speakers' bureau of Eli Lilly, Janssen Cilag, Neuraxpharm (Langenfeld, Germany), Roche, Servier, and Trommsdorf (Aachen, Germany). He has received grant support from Boehringer Ingelheim and Roche. He is co-founder of Mind and Brain Institute GmbH (Zornheim, Germany) and Brainfoods GmbH (Zornheim, Germany). Dr. Veselinović, Dr. Janouschek, Prof. Cumming, Dr. Paulzen, and Dr. Mottaghy declare no conflicts of interest.

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