Published in final edited form as:

Schizophr Res. 2015 May ; 164(0): 263–267. doi:10.1016/j.schres.2015.02.020.

Dopamine D_{2/3} Receptor Availability in the Striatum of Antipsychotic-Free Older Patients with Schizophrenia - A [¹¹C]-raclopride PET Study

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Contributors: D. Mamo, A. Graff-Guerrero, B. Mulsant, and H. Uchida led the study design. D. Mamo, A. Graff-Guerrero, S. Nakajima, T. Suzuki, and H. Uchida conducted the literature review and the acquisition of data. A. Graff-Guerrero, S. Nakajima, and F. Caravaggio analyzed and interpreted the data, and prepared the manuscript. All authors contributed to and approved to submit its current version of the manuscript.

Disclosure/Potential Conflict of Interest: Dr. Nakajima has received fellowship grants from the Canadian Institutes of Health Research (CIHR), Japan Society for the Promotion of Science, and Nakatomi Foundation, and manuscript fees from Dainippon Sumitomo Pharma and Kyowa Hakko Kirin. Dr. Mamo has received investigator-initiated grant support from Pfizer. Dr. Gerretsen has received fellowship support from the CAMH Foundation, Ontario Mental Health Foundation (OMHF), and CIHR. Dr. Uchida has received grants from Astellas Pharmaceutical, Eisai, Otsuka Pharmaceutical, GlaxoSmithKline, Shionogi, Dainippon-Sumitomo Pharma, Eli Lilly, Mochida Pharmaceutical, Meiji-Seika Pharma, and Yoshitomi Yakuhin and speaker's honoraria from Otsuka Pharmaceutical, Eli Lilly, Shionogi, GlaxoSmithKline, Yoshitomi Yakuhin, Dainippon-Sumitomo Pharma, Meiji-Seika Pharma, Abbvie, MSD, and Janssen Pharmaceutical. Dr. Suzuki has received speaker or manuscript fees from Astellas, Dainippon Sumitomo, Eli Lilly, Elsevier Japan, Janssen, Otsuka, and Weily Japan. Dr. Mulsant currently receives research funding from Brain Canada, the CAMH Foundation, the Canadian Institutes of Health Research, and the US National Institute of Health (NIH). During the past five years, he also received research support from Bristol-Myers Squibb (medications for a NIH-funded clinical trial), Eli-Lilly (medications for a NIH-funded clinical trial), and Pfizer (medications for a NIH-funded clinical trial). He directly own stocks of General Electric (less than \$5,000). Dr. Graff-Guerrero has received research support from the following external funding agencies: the CIHR, US NIH, OMHF, Brain and Behavior Research Foundation (BBRF), Mexico ICyTDF, CONACyT, and W. Garfield Weston Foundation. Other authors have no financial or other relationship relevant to the subject of this manuscript.

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Abstract

Background—No study has examined dopamine D_{2/3} receptor (D_{2/3}R) availability in antipsychotic-free older patients with schizophrenia.

Methods—We included patients with schizophrenia 50 years or older who were antipsychotic-free for at least 3 months. We compared non-displaceable binding potential (BP_{ND}) of [¹¹C]-raclopride in the caudate, putamen, ventral striatum, and globus pallidus between patients and age- and sex-matched healthy controls.

Results—Ten patients participated (antipsychotic-naïve=4). No differences in BP_{ND} were found between patients and controls in any ROIs ($F(1, 72)=.42, p=.52$).

Conclusion—The preliminary results suggest no differences in D_{2/3}R availability between antipsychotic-free older patients with schizophrenia and controls.

Keywords

schizophrenia; aging; dopamine; PET; D_{2/3} receptor

Introduction

Antipsychotics exert their effects mostly by blocking dopamine D_{2/3} receptors (D_{2/3}R). Aging is associated with increased adverse effects of antipsychotics including extrapyramidal symptoms (EPS) (Caligiuri et al., 1999). Age-related decrease in striatal D_{2/3}R availability, which may be also influenced by lifetime environmental or medical history (Nader and Czoty, 2005), would be expected to result in an increased sensitivity to antipsychotics in older patients (Uchida et al., 2009).

Several *in vivo* brain imaging studies suggest that striatal D_{2/3}R availability decreases with age in healthy humans (Backman et al., 2006), a finding we recently replicated with [¹¹C]-raclopride (Nakajima et al., In submission). Talvik et al. found that striatal D_{2/3}R availability decreased by 7–8% per decade in antipsychotic-naïve patients with schizophrenia (age=28.8±10.2 years) (Talvik et al., 2006). Wong et al. also observed similar age-related decreases in caudal D_{2/3}R availability (8–9%) between antipsychotic-naïve patients (age=45±24 years) and healthy controls (HC) (Wong et al., 1997a). Similarly, Nordström et al. found that age-dependent decreases in putamen-to-cerebellum ratios did not differ between antipsychotic-naïve younger patients (age=24.3 [18–29] years) and HC (Nordström et al., 1992). Collectively, these findings suggest that striatal D_{2/3}R availability decreases with age in patients with schizophrenia in a similar magnitude to that seen in HC. However, the age range of subjects in these studies is not wide enough to examine this issue in older patients with schizophrenia.

Despite its clinical relevance, no study has investigated D_{2/3}R availability exclusively in older patients with schizophrenia. Thus, using [¹¹C]-raclopride, we addressed this issue among those who were 50 and older and had not received antipsychotics for at least 3 months to compare striatal D_{2/3}R availability between antipsychotic-free older patients with schizophrenia and age- and sex-matched HC. We also explored relationships between D_{2/3}R availability and clinical symptoms, such as positive and negative symptoms, and adverse effects in the former population.

Materials and Methods

All procedures of this cross-sectional [¹¹C]-raclopride PET study were approved by the Centre for Addiction and Mental Health (CAMH) Research Ethics Board and complied with the 1975 Helsinki Declaration (5th revision, 2000). The study was conducted following completion of informed consent procedure at CAMH between 2008 and 2014.

Subjects

Patients were outpatients aged 50 years and older diagnosed with either schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (American Psychiatric Association, 1994). The patients were antipsychotic-free for at least 3 months and were excluded if they had been exposed to depot antipsychotics.

HC were right-handed and free of any major medical or psychiatric disorder as determined by the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) and electrocardiography.

Both patients and controls were excluded if they had a current diagnosis of substance use disorders, history of clinically unstable or life-threatening physical illness, were pregnant or lactating women, or had metal implants.

The HC were 10 volunteers (5 females; age=63.0±9.2 [48–73] years). No difference was found in age between both patients and controls ($t(18)=0.64$, $p=.53$).

Pre-scan Clinical Assessments

Clinical assessments included the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Assessments for extrapyramidal symptoms included the Simpson-Angus Scale (SAS) (Simpson and Angus, 1970), Barnes Rating Scale for Drug-Induced Akathisia (BAS) (Barnes, 1989), and Abnormal Involuntary Movement Scale (AIMS) (Lingjaerde et al., 1987). The Cumulative Illness Rating Scale for Geriatrics (CIRS-G) was used to assess comorbid physical illness at the screening visit (Miller et al., 1992).

Positron Emission Tomography Imaging with [¹¹C]-raclopride

The radiosynthesis of [¹¹C]-raclopride and the acquisition of PET images, has been described in detail elsewhere (Graff-Guerrero et al., 2010; Wilson et al., 2000). Briefly, images were acquired with the use of a high-resolution, head-dedicated PET camera system

(CPS-HRRT; Siemens Molecular Imaging, Munich, Germany), which measures radioactivity in 207 brain slices with a thickness of 1.2 mm each. The in-plane resolution was ~2.8 mm full-width at half-maximum. Transmission scans were acquired using a ^{137}Cs ($T_{1/2}=30.2$ years, energy=662 KeV) single-photon point source to provide attenuation correction; emission data were acquired in list mode. The raw data were reconstructed by filtered back-projection. [^{11}C]-raclopride data were acquired for 60 minutes and redefined into 28 frames. No differences were found in the radioactivity dose, specific activity, or injected mass of [^{11}C]-raclopride between both groups. Participants also provided a magnetic resonance imaging (MRI), acquired either on a 1.5T or a 3T Signa-GE scanner, used for coregistration of the PET scans.

Image Analysis

The region of interest (ROI)-based analysis for [^{11}C]-raclopride has been described in detail elsewhere (Graff-Guerrero et al., 2008). Briefly, time-activity curves (TACs) from ROIs were obtained from dynamic PET images in native space with reference to each subject's coregistered MRI. The coregistration of each subject's MRI to PET space was performed using the normalized mutual information algorithm in SPM2 (The Wellcome Department of Cognitive Neurology, London) (Studholme et al., 1997). The TACs were analyzed using the Simplified Reference Tissue Method (SRTM), with the cerebellum as the reference region, deriving a quantitative estimate of binding: non-displaceable binding potential (BP_{ND}) (Lammertsma and Hume, 1996). The basis function implementation of the SRTM was applied to dynamic PET images to generate parametric voxelwise BP_{ND} maps using PMOD (v2.7; PMOD Technologies, Zurich, Switzerland) (Gunn et al., 1997). These images were spatially normalized into the Montreal Neurological Institute (MNI) brain space by nearest neighbour interpolation with a voxel size fixed in $2 \times 2 \times 2 \text{ mm}^3$ using SPM2. Regional BP_{ND} estimates were then derived from ROIs defined in MNI space. The striatum and globus pallidus (GP) were defined according to Mawlawi et al (Mawlawi et al., 2001) and Tziortzi et al (Tziortzi et al., 2011), respectively.

Statistical Analysis

The analysis was performed using the SPSS (version 12.0; SPSS, Chicago, IL). BP_{ND} is presented as mean $\pm$ SD. Analysis of variance was performed to compare BP_{ND} s between patients and healthy controls per ROI. In exploratory analyses, considering potential up-regulation of $\text{D}_{2/3}\text{R}$ (Howes et al., 2012), BP_{ND} was compared between antipsychotic-naïve or antipsychotic-free patients, and HC, as well as between antipsychotic-naïve and antipsychotic-free patients by Mann-Whitney U tests. We explored Pearson's product moment correlations between BP_{ND} and PANSS, BPRS, AIMS, BAS, and SAS scores. The significance was assumed at a $p < .05$ (two-tailed).

Results

Demographic and clinical characteristics of the ten patients are summarized in Table 1.

BP_{ND} in each region is summarized in Figure 1 and Table 2. No differences were found between patients and HC in BP_{ND} in any ROIs irrespective of antipsychotic treatment

history. We found no differences in BP_{ND} in any ROIs between antipsychotic-naïve and antipsychotic-free patients (all p 's > .05).

No correlation was found between [¹¹C]-raclopride BP_{ND} and PANSS total or subscale scores or those of extrapyramidal symptoms (Table 3).

Discussion

To our knowledge, this study demonstrated for the first time that there were no differences in D_{2/3}R availability in the basal ganglia between older patients with schizophrenia and HC, irrespective of antipsychotic treatment history. The most recent meta-analysis noted no difference in D_{2/3}R availability in antipsychotic-naïve younger patients with schizophrenia and controls (Howes et al., 2012). Our finding extends the age range (up to 83 years) of patients whose D_{2/3}R availability in the basal ganglia is similar to HC. It has been reported that age-related decreases in D_{2/3}R availability in the striatum are similar between patients with schizophrenia and HC (Nordström et al., 1992; Wong et al., 1997b). Extending the age range, our findings corroborate these prior observations.

Aging is associated with increased adverse consequences of antipsychotics including EPS. Since EPS depend on both antipsychotic doses and D_{2/3}R occupancy in the striatum (Caligiuri et al., 1999), our findings suggest that increased sensitivity to antipsychotics in older patients with schizophrenia may be attributable to age-related decreases in D_{2/3}R availability. On the other hand, clinical outcomes have been reported to improve with increasing age in patients with early-onset schizophrenia (Jeste and Maglione, 2013), including diminished psychotic symptoms and improved psychosocial function (Jeste et al., 2011). Our group has previously demonstrated that the therapeutic window of D_{2/3}R occupancy with antipsychotics in older patients with schizophrenia may be 10% lower than that of 65%–80% often reported in younger patients (Graff-Guerrero et al., 2014). Thus, antipsychotic dosing might be lowered for relapse prevention in light of age-related decreases in D_{2/3}R availability in order to prevent side effects.

Our study must be interpreted in light of its limitations. First, the sample size was small, which did not allow us to examine effects of lifetime environmental or medical history on D_{2/3}R availability. Second, 6 subjects were antipsychotic-free patients who may have potentially up-regulated D_{2/3}R (Howes et al., 2012). Finally, this study included 2 patients with late-onset schizophrenia, whose pathophysiology may be different from early-onset schizophrenia.

In conclusion, this [¹¹C]-raclopride PET study indicates no differences in D_{2/3}R availability in the basal ganglia between antipsychotic-free older patients with schizophrenia and age- and sex-matched HC. Further research is required to determine how age-related changes in D_{2/3}R in these patients influence optimal antipsychotic dosing.

Acknowledgments

We thank the PET Centre staff at the Centre for Addiction and Mental Health, including Alvina Ng and Laura Nguyen, for technical assistance in data collection. We also thank Kathryn Kalahani-Bargis, Zhe Feng, Thushanthi

Balakumar, Alex Naber, Ausmeema Hossain, and Danielle Uy for their assistance in participant recruitment and data administration.

Role of Funding Source: This study was supported by the Canadian Institutes of Health Research (MOP-97946) (MOP-114989) (Drs. Graff-Guerrero and Mamo) and the US National Institutes of Health (RO1MH084886) (Drs. Graff-Guerrero and Mamo).

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Figure 1a.

Figure 1b.

Figure 1. Comparison of [¹¹C]-raclopride binding in every region of interest between antipsychotic-free older patients with schizophrenia and age- and sex-matched healthy controls

Figure 1a. Comparison of [¹¹C]-raclopride binding in every region of interest between antipsychotic-free older patients with schizophrenia and healthy controls.

Figure 1b. Comparison of [¹¹C]-raclopride binding in every region of interest between antipsychotic-naïve older patients with schizophrenia and healthy controls.

No differences were found between patients and age- and sex-matched healthy controls in BP_{ND} in any ROIs (1a). There were no differences in BP_{ND} in any ROIs between antipsychotic-naïve patients and healthy controls (1b).

Abbreviations: BP_{ND} = non-displaceable binding potentials, Cau = caudate, GP = globus pallidus HC = healthy controls, Pt = patients with older schizophrenia, Put = putamen, VS = ventral striatum

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Table 1

Demographic and clinical characteristics of the patients

Characteristics	Entire sample (N = 10)	Antipsychotic-naïve patients (N = 4)	Antipsychotic-free patients (N = 6)
Age, mean $\pm$ SD (range) (years)	66.1 $\pm$ 12.2 (50 – 83)	66.5 $\pm$ 13.0 (52 – 83)	66.3 $\pm$ 11.7 (50 – 81)
Females, N (%)	5 (50.0)	1 (10.0)	4 (40.0)
Diagnosis			
Schizophrenia, N (%)	7 (70.0)	4 (40.0)	3 (30.0)
Schizoaffective disorder, N (%)	3 (30.0)	0 (0.0)	3 (30.0)
Age of onset, mean $\pm$ SD (range) (years)	31.2 $\pm$ 16.5 (8 – 68)	38.8 $\pm$ 24.8 (8 – 68)	26.9 $\pm$ 9.3 (18 – 40)
Duration of illness, mean $\pm$ SD (range) (years)	33.7 $\pm$ 18.4 (1.0 – 52.0)	27.8 $\pm$ 22.2 (1.0 – 48.0)	39.4 $\pm$ 15.6 (11.0 – 52.0)
Duration of untreated illness, mean $\pm$ SD (range) (years)	12.5 $\pm$ 18.6 (0.3 – 48.0)	27.8 $\pm$ 22.2 (1.0 – 48.0)	2.0 $\pm$ 3.6 (0.3 – 10.0)
Number of Psychotic Episodes	4.0 $\pm$ 3.5 (1 – 10)	1.3 $\pm$ 0.5 (1 – 2)	5.0 $\pm$ 3.0 (1 – 10)
Number of Hospitalization	3.8 $\pm$ 3.2 (0 – 10)	1.3 $\pm$ 0.8 (0 – 2)	5.3 $\pm$ 3.2 (2 – 10)
Clinical symptoms			
PANSS total score	82.6 $\pm$ 28.8	79.8 $\pm$ 22.6	84.1 $\pm$ 33.5
PANSS Positive subscale score	23.2 $\pm$ 9.3	23.8 $\pm$ 5.9	22.9 $\pm$ 11.3
PANSS Negative subscale score	19.8 $\pm$ 7.5	18.8 $\pm$ 4.8	20.4 $\pm$ 8.0
PANSS General			
Psychopathology subscale score	39.6 $\pm$ 13.8	37.3 $\pm$ 12.7	40.9 $\pm$ 15.3
BPRS total score	55.4 $\pm$ 19.1	53.8 $\pm$ 15.8	56.3 $\pm$ 21.9
CIRS-G severity score	2.2 $\pm$ 1.0	2.5 $\pm$ 1.3	2.0 $\pm$ 0.9
Extrapyramidal symptoms			
AIMS total score	0.8 $\pm$ 2.1	0.3 $\pm$ 0.5	1.1 $\pm$ 2.6
BAS total score	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
SAS total score	0.7 $\pm$ 0.9	0.5 $\pm$ 0.6	0.9 $\pm$ 1.1

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Rating Scale for Drug-Induced Akathisia, BPRS = Brief Psychiatric Rating Scale, CIRS-G = Cumulative Illness Rating Scale-Geriatric, PANSS = Positive and Negative Syndromes Scale, SAS = Simpson-Angus Scale.

Table 2

Non-displaceable binding potential in each region of interest

	Patients with schizophrenia	Healthy controls	Statistics	Antipsychotic-naïve patients	Healthy controls	Statistics	Antipsychotic-free patients	Healthy controls	Statistics
Caudate	3.13 ± 0.63	2.88 ± 0.37	F(3, 72) = .65, p = .59 for interaction	3.27 ± 0.68	2.94 ± 0.52	U = 6.00, p = .56	3.04 ± 0.63	2.84 ± 0.27	U = 18.00, p = 1.00
Putamen	3.97 ± 0.52	4.08 ± 0.38	between diagnosis and ROI; F(1, 72) = .42, p = .52 for diagnosis	4.07 ± 0.41	4.17 ± 0.22	U = 6.00, p = .56	3.90 ± 0.62	4.02 ± 0.48	U = 13.00, p = .42
VS	3.05 ± 0.19	3.07 ± 0.39		3.01 ± 0.21	3.11 ± 0.42	U = 6.00, p = .56	3.08 ± 0.19	3.05 ± 0.41	U = 16.00, p = .75
GP	2.19 ± 0.39	2.04 ± 0.56		2.35 ± 0.54	2.21 ± 0.41	U = 6.00, p = .56	2.08 ± 0.26	1.93 ± 0.66	U = 9.00, p = 0.15

Abbreviations: GP = globus pallidus, VS = ventral striatum

Table 3
Relationships between [^{11}C]-raclopride BP_{ND} and clinical symptoms and extrapyramidal symptoms

	[^{11}C]-raclopride BP _{ND}			
	Caudate	Putamen	VS	GP
Clinical symptoms				
PANSS total score				
r	.37	.42	-.38	-.04
p	.29	.23	.27	.91
PANSS Positive subscale score				
r	.25	.36	-.53	-.03
p	.49	.31	.11	.93
PANSS Negative subscale score				
r	.18	.24	-.48	-.01
p	.63	.51	.16	.97
PANSS General Psychopathology subscale score				
r	.45	.56	-.45	-.09
p	.19	.09	.20	.80
BPRS total score				
r	.37	.47	-.46	-.05
p	.29	.17	.18	.89
Extrapyramidal symptoms				
AIMS total score				
r	-.56	-.52	-.37	-.27
p	.09	.13	.29	.45
BAS total score				
r	N/A	N/A	N/A	N/A
p	N/A	N/A	N/A	N/A
SAS total score				
r	-.22	-.50	-.21	.18
p	.54	.14	.56	.62

Pearson's product moment correlations between clinical symptoms and extrapyramidal symptoms and BPND in each ROI were explored.

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Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BAS = Barnes Rating Scale for Drug-Induced Akathisia, BPND = non-displaceable binding potential, BPRS = Brief Psychiatric Rating Scale, GP = globus pallidus, PANSS = Positive and Negative Syndromes Scale, SAS = Simpson-Angus Scale, VS = ventral striatum.