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Effects of image reconstruction algorithm on neurotransmission PET studies in humans: comparison between filtered backprojection and ordered subsets expectation maximization

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Objectives: Both reconstruction algorithms, filtered backprojection (FBP) and ordered subsets expectation maximization (OSEM), are widely used in clinical positron emission tomography (PET) studies. Image reconstruction for most neurotransmission PET scan data is performed by FBP, while image reconstruction for whole-body [^{18}F]FDG scan data is usually performed by OSEM. Although several investigators have compared FBP and OSEM in terms of the quantification of regional radioactivity and physiological parameters calculated from PET data, only a few studies have compared the two reconstruction algorithms in PET studies that estimate neurotransmission, i.e., neuroreceptor and neurotransporter binding. In this study we compared mean regional radioactivity concentration in the late phase and binding potential (BP) between FBP and OSEM algorithms in neurotransmission PET studies for [^{11}C]raclopride and [^{11}C]DASB. ***Methods:*** Dynamic PET scans with [^{11}C]raclopride in 3-dimensional mode were performed on seven healthy subjects. Dynamic PET scans with [^{11}C]DASB in 2-dimensional mode were performed on another seven subjects. OSEM images were post-filtered so that its transverse spatial resolution became similar to that of FBP with the same Hanning filter (Kernel FWHM 6 mm). In both PET studies we calculated the BP of [^{11}C]raclopride and [^{11}C]DASB by a reference tissue model for each ROI (region of interest). ***Results:*** There was no significant difference in mean regional radioactivity concentration between FBP and OSEM for [^{11}C]raclopride and [^{11}C]DASB. Only +2.4 – +3.2%, but still a significant difference in BP of [^{11}C]raclopride between FBP and OSEM was observed in the striatum. There was no significant difference in BP between FBP and OSEM in other than the striatum for [^{11}C]raclopride and in all regions for [^{11}C]DASB. In addition, there was no significant difference in root mean square error between FBP and OSEM when BP was calculated. ***Conclusions:*** The BP values were similar between FBP and OSEM algorithms with [^{11}C]raclopride and [^{11}C]DASB. This study indicates that OSEM can be used for human neurotransmission PET studies for calculating BP although OSEM was not necessarily superior to FBP in the present study.

Key words: FBP, OSEM, PET, [^{11}C]raclopride, [^{11}C]DASB

INTRODUCTION

Both reconstruction algorithms, filtered backprojection (FBP) and ordered subsets expectation maximization (OSEM), are widely used in clinical positron emission tomography (PET) studies. FBP is based on the projection slice theorem.[1] Because of its rapid calculation speed, FBP has been the standard reconstruction method for brain PET study although it is susceptible to artifacts.[1] OSEM was developed by Hudson and Larkin[2] as a reasonably fast computation method based on the maximum likelihood expectation maximization (MLEM) algorithm, and that it was superior to FBP in detecting focal regions.[3] Iterative reconstruction methods based on MLEM have

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been successfully used to improve quality because they can deal with an accurate system model and Poisson noise characteristics with non-negative constraint. For example, it has been reported that MLEM is superior to FBP in detecting focal regions.[4] Therefore, OSEM has the potential of improving the accuracy of dynamic PET analyses. Recently, OSEM has been widely used in whole-body [^{18}F]FDG studies for detecting tumor lesions.

Several studies have comparatively investigated FBP and OSEM in PET studies. OSEM was reported to be superior to FBP in detecting focal regions in phantom studies using [^{18}F]FDG and [^{15}O]water.[5,6] [^{18}F]FDG studies in brain and cardiac PET showed that the quantitative accuracy of OSEM was similar to that of FBP.[7–9] Another study using [^{11}C]WAY100635 for 5-HT$_{1A}$ receptor showed a positive bias of OSEM for distribution volume in the cerebellum and a negative bias of FBP for radioactivity concentration in regions with low activities less than 0.05 kBq/cm^3.[10] To our knowledge, there has been no study comparing neuroreceptor binding between FBP and OSEM in a human PET study.

In this study we compared regional radioactivity concentration and binding potential (BP) as an index of receptor binding between FBP and OSEM algorithms in neurotransmission PET studies with [^{11}C]raclopride, a radioligand for dopamine D$_2$ receptor in the striatum,[11] and with [^{11}C]DASB, a radioligand for serotonin transporter in the thalamus, striatum, and cerebral cortex.[12,13]

MATERIALS AND METHODS

Subjects

PET scanning with [^{11}C]raclopride was performed on seven healthy subjects (five males and two females), aged 27.0 ± 5.4 years (mean ± SD), and PET scanning with [^{11}C]DASB was performed on a different seven healthy subjects (four males and three females), aged 41.9 ± 7.6 years. There was no overlapping of subjects between the two PET studies. This study was approved by the ethics and radiation safety committees of the National Institute of Radiological Sciences, Chiba, Japan. Written informed consent was obtained from each subject.

PET and MRI procedures

PET scanning was carried out using CTI-Siemens ECAT EXACT HR+ (CTI-Siemens, Knoxville, Tenn., USA), providing contiguous 63 planes and a 15.5-cm field of view.[14] The matrix of transverse plane was 128 × 128 (2.7 × 2.7 mm) and the slice thickness was 2.4 mm. To minimize head movement during the brain scans, a head fixation device with an individual mouthpiece was used (Fixster Instruments, Stockholm, Sweden). A 10-min pre-injection transmission scan was performed with a ^{68}Ge-^{68}Ga source to correct for attenuation.

In the [^{11}C]raclopride study, 90-min dynamic PET brain scans were obtained. Data were acquired in 3-dimensional (3D) mode. The injected dose was 224.9 ± 18.7 MBq and the specific radioactivity at the time of injection was 150.0 ± 45.7 MBq/nmol. A total of 43 serial frames were acquired using the following imaging sequence: 20 sec × 12, 1 min × 16, 4 min × 10, 6 min × 5.

In the [^{11}C]DASB study, 90-min dynamic PET brain scans were obtained. Data were acquired in 2-dimensional (2D) mode. The injected doses were 170.2 ± 56.1 MBq and the specific radioactivities at the time of injection were 707.6 ± 108.1 MBq/nmol. A total of 27 serial frames were acquired using the following imaging sequence: 1 min × 4, 2 min × 13, 4 min × 5, 5 min × 8.

A magnetic resonance imaging (MRI) study was performed using Philips Intera, 1.5 tesla (Philips Medical Systems, Best, The Netherlands) for all subjects. T1 images with a 1-mm thick transverse plane were obtained (repetition time [TR]/echo time [TE] 21/9.2 milliseconds, flip angle 30°, matrix 256 × 256, field of view [FOV] 256 mm × 256 mm).

Image reconstruction

All PET images were reconstructed using both FBP (Hanning filter, Kernel 6 mm) and OSEM (6 iterations, 16 subsets) as recommended by CTI-Siemens and used in previous studies.[6,7] The same Hanning filter with Kernel 6 mm in full width at half maximum (FWHM) was used for both FBP and OSEM so that the transverse resolution of OSEM became similar to that of FBP. The 3D data of [^{11}C]raclopride were converted to 2D sinograms using Fourier rebinning (FORE).[15]

Data analyses

Circular 10-mm diameter regions-of-interest (ROIs) were set on the PET summation image. ROIs were located on the cerebellum, thalamus, putamen, caudate, frontal cortex, temporal cortex, and occipital cortex for three serial frames as shown in Figure 1, referring to T1-weighted MRI images. Tissue radioactivity (expressed in kBq/m*l*) in ROIs was calculated for each frame and normalized to the injected dose of radioactivities ([^{11}C]raclopride: 222 MBq, [^{11}C]DASB: 740 MBq), and plotted against time.

Calculation of binding potential (BP) and root mean square error

BP of [^{11}C]raclopride

Binding potential (BP) was defined by the following equation:

$$\mathrm{BP} = B_{\max}/K_d,$$

where $B_{\max}$ is the concentration of the binding site and K_d is the dissociation constant for the radioligand. BP of [^{11}C]raclopride were calculated by simplified reference tissue model.[16] This model also allows the estimation of BP as follows:

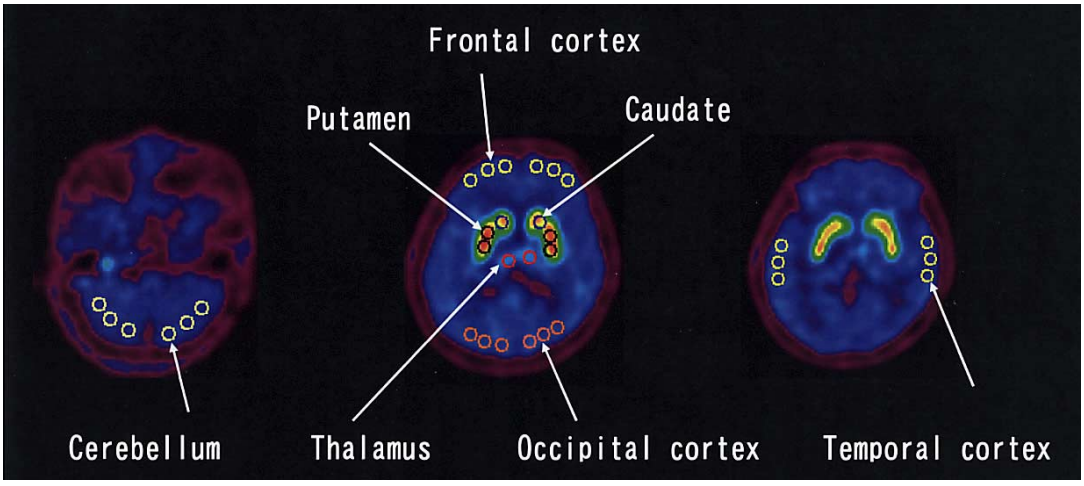

Fig. 1 Location of regions of interest (ROIs) on the summation image of [^{11}C]raclopride. Circular 10-mm diameter ROIs were set on the PET summation image. ROIs were located on the cerebellum, thalamus, putamen, caudate, frontal cortex, temporal cortex, and occipital cortex for three serial frames, referring to T1-weighted MRI images.

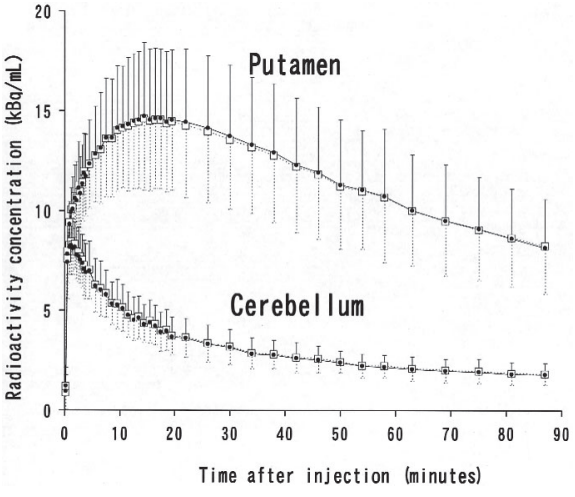

Fig. 2 Time-activity curves (TACs) of [^{11}C]raclopride in putamen and cerebellum (mean ± SD, n = 7). FBP data are shown in white squares and dotted lines and OSEM data are shown in black circles and solid lines. Tissue radioactivity (expressed in kBq/m*l*) in ROIs was calculated for each frame and normalized to the injected dose of radioactivities ([^{11}C]raclopride: 222 MBq, [^{11}C]DASB: 740 MBq), and plotted against time.

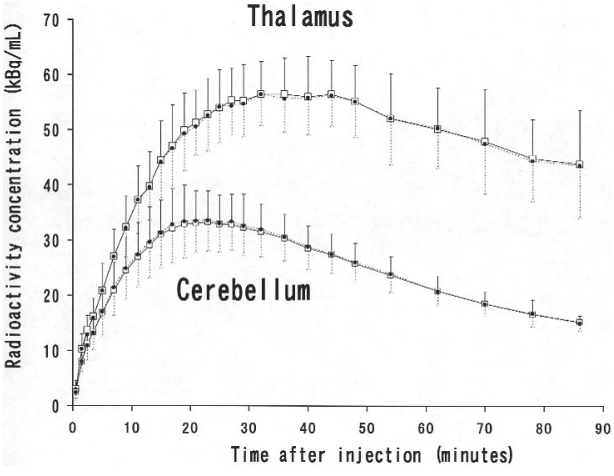

Fig. 3 Time-activity curves (TACs) of [^{11}C]DASB in thalamus and cerebellum (mean ± SD, n = 7). FBP data are shown in white squares and dotted lines and OSEM data are shown in black circles and solid lines. Tissue radioactivity (expressed in kBq/m*l*) in ROIs was calculated for each frame and normalized to the injected dose of radioactivities ([^{11}C]raclopride: 222 MBq, [^{11}C]DASB: 740 MBq), and plotted against time.

$$C_t(t) = R_1 C_r(t) + \{k_2 - R_1 k_2/(1 + \mathrm{BP})\} C_t(t) \otimes \exp\{-k_2 t/(1 + \mathrm{BP})\}$$

where $C_t(t)$ is regional radioactivity of target tissue, $C_r(t)$ is radioactivity of reference tissue, R_1 is the ratio of the influx rate from blood to brain in the ROI tissue to that in the reference region, k_2 is the kinetic constant for ligand transfer from tissue to blood, and ⊗ is the convolution symbol. The cerebellum was used as a reference region because the densities of dopamine D_2 receptor have been confirmed to be negligible in the cerebellum.[11,17]

BP of [^{11}C]DASB

BP of [^{11}C]DASB was calculated by multilinear reference tissue model 2 (MRTM2) as follows:[13]

$$C_t(T) = -\frac{V_R}{b}\left(\int_0^T C_r(t)dt + \frac{1}{k_2^r} C_t(T)\right) + \frac{1}{b}\int_0^T C_t(t)dt$$

where V_R is the distribution volume (DV) of target tissue divided by DV of reference tissue, b is a constant, and k_2^r is the clearance rate constant from the reference region.

BP is calculated as follows:

$$BP = V_R - 1$$

In this study, the cerebellum was used as the reference tissue because of its negligible density of serotonin transporter.[18–20]

Root mean square error

To evaluate conditions of reference tissue model analyses, root mean square error in calculating the BP of [^{11}C]raclopride and [^{11}C]DASB is calculated as follows:

$$\text{Root mean square error} = \sqrt{\Sigma\,(C_f - C_m)^2/N}$$

where C_f is model fitted radioactivity, C_m is measured radioactivity, and N is the number of frame.

Calculation of mean regional radioactivity concentrations in the late phase

To investigate the effects of reconstruction algorithms on regional radioactivity concentration, mean regional radioactivitiy concentrations in the late phase with decay correction were calculated. The mean regional radioactivitiy concentration of [^{11}C]raclopride is the value of the area under the curve of time-radioactivity concentration from 30 to 90 min divided by 60 min, and that of [^{11}C]DASB is the value of the area under the curve of time-radioactivity concentration from 40 to 90 min divided by 50 min.

Calculation of percent difference

Percent differences in mean regional radioactivitiy concentrations and in BP between FBP and OSEM for [^{11}C]raclopride and [^{11}C]DASB were calculated as follows:

$$\text{Percent difference } (\%) = 100 \times (A_{OSEM} - A_{FBP})/A_{FBP}$$
$$\text{Percent difference } (\%) = 100 \times (BP_{OSEM} - BP_{FBP})/A_{FBP}$$

where A_{OSEM} is the mean regional radioactivitiy concentrations by OSEM, A_{FBP} is the mean regional radioactivitiy concentrations by FBP, BP_{OSEM} is BP by OSEM, and BP_{FBP} is BP by FBP.

Statistical analysis

Statistical analysis to clarify the difference of mean regional radioactivitiy concentrations between FBP and OSEM for [^{11}C]raclopride and [^{11}C]DASB was performed using a two-way repeated analysis of variance (ANOVA); between: reconstruction [FBP/OSEM]; within: region [putamen/caudate/thalamus/frontal cortex/temporal cortex/occipital cortex/cerebellum] with multiple comparisons of Bonferroni. Statistical analysis to clarify the difference in BP and in root mean square error between FBP and OSEM for [^{11}C]raclopride and [^{11}C]DASB was performed using a two-way repeated ANOVA; between: reconstruction [FBP/OSEM]; within: region [putamen/caudate/thalamus/frontal cortex/temporal cortex/occipital cortex] with multiple comparisons of Bonferroni. $P < 0.05$ was considered statistically significant. All numerical data were expressed as mean ± SD.

Table 1 Mean regional radioactivity concentrations for [^{11}C]raclopride (kBq/m*l*)

	FBP	OSEM	Percent difference (%)
putamen	11.0 ± 3.03	11.0 ± 3.07	+0.6 ± 0.3
caudate	9.97 ± 2.55	10.1 ± 2.59	+1.1 ± 0.3
thalamus	3.51 ± 1.01	3.45 ± 1.08	–0.9 ± 0.9
occipital	3.10 ± 0.91	3.08 ± 0.91	–0.8 ± 0.7
temporal	3.03 ± 0.85	3.00 ± 0.85	–0.9 ± 0.6
frontal	2.74 ± 0.73	2.73 ± 0.76	–0.6 ± 1.5
cerebellum	2.37 ± 0.67	2.34 ± 0.66	–1.2 ± 1.3

There was no statistically significant difference in any region between FBP and OSEM. Percent difference (%) = 100 × (A_{OSEM} – A_{FBP})/A_{FBP}; A_{OSEM} = mean regional radioactivitiy concentrations by OSEM, A_{FBP} = mean regional radioactivitiy concentrations by FBP.

Table 2 Mean regional radioactivity concentrations for [^{11}C]DASB (kBq/m*l*)

	FBP	OSEM	Percent difference (%)
thalamus	51.4 ± 8.9	51.2 ± 9.1	–0.4 ± 1.3
putamen	49.4 ± 8.3	49.3 ± 8.4	–0.4 ± 0.9
caudate	47.7 ± 8.6	47.5 ± 9.1	–0.5 ± 2.1
occipital	26.8 ± 5.3	26.7 ± 5.3	–0.4 ± 0.6
temporal	27.0 ± 5.5	27.2 ± 6.0	+0.4 ± 1.0
frontal	24.7 ± 5.0	25.1 ± 5.2	+1.2 ± 1.2
cerebellum	21.0 ± 4.1	21.1 ± 4.3	0.0 ± 0.0

There was no statistically significant difference in any region between FBP and OSEM. Percent difference (%) = 100 × (A_{OSEM} – A_{FBP})/A_{FBP}; A_{OSEM} = mean regional radioactivitiy concentrations by OSEM, A_{FBP} = mean regional radioactivitiy concentrations by FBP.

RESULTS

Time-activity curves (TACs) with decay correction of [^{11}C]raclopride (putamen and cerebellum) and [^{11}C]DASB (thalamus and cerebellum) are shown in Figure 2 and Figure 3, respectively. The shape of TACs was almost the same between FBP and OSEM for both [^{11}C]raclopride and [^{11}C]DASB. In the last frame of the dynamic scans, regional radioactivity concentrations without decay corrections were 0.08 kBq/m*l* for [^{11}C]raclopride and 0.44 kBq/m*l* for [^{11}C]DASB.

Mean regional radioactivitiy concentrations in the late phase of [^{11}C]raclopride and [^{11}C]DASB are shown in Tables 1 and 2, respectively. There was no statistically significant difference in mean regional radioactivity concentrations between FBP and OSEM. The percent difference in mean regional radioactivity concentrations

Table 3 Binding potentials for [^{11}C]raclopride

	FBP	OSEM	Percent difference (%)
putamen	3.09 ± 0.16	3.16 ± 0.16	+2.4 ± 0.7*
caudate	2.75 ± 0.18	2.84 ± 0.17	+3.2 ± 0.8*
thalamus	0.45 ± 0.10	0.45 ± 0.10	+1.2 ± 2.6
occipital	0.28 ± 0.04	0.28 ± 0.04	+2.0 ± 3.7
temporal	0.26 ± 0.04	0.27 ± 0.04	+2.4 ± 2.6
frontal	0.17 ± 0.03	0.19 ± 0.02	+9.5 ± 10.7

*$p < 0.05$, ANOVA with multiple comparisons of Bonferroni. Percent difference (%) = 100 × (BP_{OSEM} − BP_{FBP})/BP_{FBP}; BP_{OSEM} = BP by OSEM, BP_{FBP} = BP by FBP.

Table 4 Binding potentials for [^{11}C]DASB

	FBP	OSEM	Percent difference (%)
thalamus	1.50 ± 0.25	1.49 ± 0.26	−1.0 ± 2.0
putamen	1.49 ± 0.22	1.48 ± 0.24	−1.0 ± 4.6
caudate	1.43 ± 0.26	1.43 ± 0.31	−0.4 ± 6.3
occipital	0.24 ± 0.05	0.23 ± 0.05	−4.7 ± 7.6
temporal	0.25 ± 0.06	0.25 ± 0.06	−0.2 ± 5.2
frontal	0.14 ± 0.05	0.15 ± 0.05	+7.5 ± 6.4

There was no statistically significant difference in any region between FBP and OSEM. Percent difference (%) = 100 × (BP_{OSEM} − BP_{FBP})/BP_{FBP}; BP_{OSEM} = BP by OSEM, BP_{FBP} = BP by FBP

between FBP and OSEM was within ±1.2% for both [^{11}C]raclopride and [^{11}C]DASB.

BP of both algorithms for [^{11}C]raclopride and [^{11}C]DASB are shown in Tables 3 and 4, respectively. Two-way repeated ANOVA a showed significant region × reconstruction interaction ($p < 0.05$) for [^{11}C]raclopride. With the multiple comparisons of Bonferroni, it was indicated that BP by OSEM was significantly higher than by FBP in the putamen ($p < 0.05$) and caudate ($p < 0.05$) for [^{11}C]raclopride. The percent difference in BP between FBP and OSEM for [^{11}C]raclopride in the putamen and in the caudate were +2.4 and +3.2%, respectively. There was no significant difference in BP between FBP and OSEM in other than the striatum for [^{11}C]raclopride and in all regions for [^{11}C]DASB. The percent difference in BP between FBP and OSEM were +7.5% and +9.5% at maximum for [^{11}C]raclopride and [^{11}C]DASB, respectively, in the frontal cortex where BP was lowest among the ROIs.

Root mean squares error for [^{11}C]raclopride and [^{11}C]DASB are shown in Tables 5 and 6, respectively. There were no significant differences in root mean square errors between FBP and OSEM for both [^{11}C]raclopride and [^{11}C]DASB.

Table 5 Root mean square error for [^{11}C]raclopride

	FBP	OSEM
putamen	0.44 ± 0.08	0.44 ± 0.08
caudate	0.49 ± 0.09	0.50 ± 0.10
thalamus	0.43 ± 0.15	0.41 ± 0.16
occipital	0.36 ± 0.05	0.34 ± 0.04
temporal	0.36 ± 0.06	0.35 ± 0.06
frontal	0.29 ± 0.04	0.29 ± 0.04

Root mean square error = $\sqrt{\Sigma (C_f - C_m)^2/N}$; C_f = model fitted radioactivity, C_m = measured radioactivity, N = the number of frames. There was no statistically significant difference in any region between FBP and OSEM.

Table 6 Root mean square error for [^{11}C]DASB

	FBP	OSEM
thalamus	1.76 ± 0.22	1.87 ± 0.28
putamen	1.33 ± 0.37	1.47 ± 0.29
caudate	1.62 ± 0.40	1.61 ± 0.25
occipital	0.79 ± 0.09	0.97 ± 0.12
temporal	0.76 ± 0.11	0.90 ± 0.12
frontal	0.77 ± 0.13	0.94 ± 0.17

Root mean square error = $\sqrt{\Sigma (C_f - C_m)^2/N}$; C_f = model fitted radioactivity, C_m = measured radioactivity, N = the number of frames. There was no statistically significant difference in any region between FBP and OSEM.

DISCUSSION

In the present study, the subjects were healthy volunteers, and therefore the result may be different from that of patients. The results of this study, namely that BP obtained by OSEM did not differ much from that by FBP, are in agreement with previous studies.[7,9] Oda et al. performed kinetic analysis on [^{18}F]FDG dynamic brain PET, determining that the mean values for K1, k2, and k3 obtained by OSEM were almost equal to those by FBP.[7] Lubberink et al. reported that there was a good correlation and little bias in [^{18}F]FDG uptake between FBP and OSEM in a cardiac PET study.[9] Our OSEM results were similar to those of FBP in neurotransmission PET studies with [^{11}C]raclopride and [^{11}C]DASB when a relatively large FWHM filter and relatively large ROIs were used as in the present study.[7,9] In addition, in the present study, the radioactivity concentrations of both [^{11}C]raclopride and [^{11}C]DASB were rather higher than 0.05 kBq/cm^3, a level at which bias between FBP and OSEM was reported to be marked.[10]

Only +2.4 – +3.2%, but still a significant difference in BP of [^{11}C]raclopride between FBP and OSEM was observed in the striatum. Because BP was calculated with the method using a reference region in this study, BP is directly affected by the change of radioactivity both in the target region and the reference region (cerebellum). In

[^{11}C]raclopride study, mean regional radioactivity concentration in the cerebellum by OSEM was smaller than that by FBP, and mean regional radioactivity concentration in the putamen and the caudate by OSEM were larger than that by FBP. These might cause a marked difference in BP between FBP and OSEM in [^{11}C]raclopride study. On the other hand, there was no significant difference in BP between FBP and OSEM for [^{11}C]DASB. The discrepancy of results between [^{11}C]raclopride and [^{11}C]DASB may be due to their regional distributions. As compared with [^{11}C]raclopride, the differences of mean regional radioactivity concentration in target regions and cerebellum between FBP and OSEM were small for [^{11}C]DASB (Tables 1, 2). In addition, differences in radioactivity between FBP and OSEM in the cerebellum and striatum for the [^{11}C]raclopride study might be caused by space-variant degradation in axial resolution due to FORE used in 3D acquisition, which converts 3D to 2D sinograms.[21]

Although it was reported that OSEM can significantly reduce image noise, especially in low count regions,[22] there was no significant difference in root mean square error between FBP and OSEM for [^{11}C]raclopride and [^{11}C]DASB in this study (Tables 5, 6). On the other hand, Koch et al. reported that OSEM was a preferable approach for a SPECT study of patients to evaluate dopamine transporter binding.[23] As Poisson noise increases when radioactivity concentration decreases, OSEM may be useful for neurotransmission PET studies.

In conclusion, the binding potentials of both radioligands are similar between FBP and OSEM algorithms in human neurotransmission PET studies. This study indicates that OSEM can be used for human neurotransmission PET studies for calculating BP although OSEM was not necessarily superior to FBP in the present study.

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