Evaluation of motion correction methods in human brain PET imaging—A simulation study based on human motion data

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Purpose: Motion correction in PET has become more important as system resolution has improved. The purpose of this study was to evaluate the accuracy of event-by-event and frame-based MC methods in human brain PET imaging.

Methods: Motion compensated image reconstructions were performed with static and dynamic simulated high resolution research tomograph data with frame-based image reconstructions, using a range of measured human head motion data. Image intensities in high-contrast regions of interest (ROI) and parameter estimates in tracer kinetic models were assessed to evaluate the accuracy of the motion correction methods.

Results: Given accurate motion data, event-by-event motion correction can reliably correct for head motions. The average ROI intensities and the kinetic parameter estimates V_T and BP_{ND} were comparable to the true values. The frame-based motion correction methods with correctly aligned attenuation map using the average of externally acquired motion data or motion data derived from image registration give comparable quantitative accuracy. For large intraframe (>5 mm) motion, the frame-based methods produced $\sim 9\%$ bias in ROI intensities, $\sim 5\%$ in V_T , and $\sim 10\%$ in BP_{ND} estimates. In addition, in real studies that lack a ground truth, the normalized weighted residual sum of squared difference is a potential figure-of-merit to evaluate the accuracy of motion correction methods.

Conclusions: The authors conclude that frame-based motion correction methods are accurate when the intraframe motion is less than 5 mm and when the attenuation map is accurately aligned. Given accurate motion data, event-by-event motion correction can reliably correct for head motion in human brain PET studies. © 2013 American Association of Physicists in Medicine. [<http://dx.doi.org/10.1118/1.4819820>]

Key words: PET, motion correction, event-by-event, dynamic, frame-based

1. INTRODUCTION

PET scanner spatial resolution has improved over the years. The high resolution research tomograph (HRRT) (Ref. 1) has a resolution of better than 3 mm. Uncorrected head motion blurs the images, reduces the measured activity in high-uptake regions, and produces inaccurate parameter estimates in tracer kinetic models. Therefore, motion correction is required if the magnitude of motion, in comparison to the image resolution, is substantial.^{2–4}

Current motion compensation methods include software-based image-registration^{5–9} and hardware motion tracking using an external measurement device.^{4,10–12} For software-based methods, i.e., frame-based image registration methods, the raw data are divided into temporal frames, each of which is reconstructed without motion correction and registered *post hoc* to a reference orientation.^{9,13,14} In this method, motion that occurs within a frame is not corrected, thus blurring the image and generating bias in kinetic parameter estimates. Montgomery *et al.* reported that intraframe motion resulted

in increased variability in regional activity and binding potential estimates in test–retest studies.⁴ Also, misalignment of the attenuation and emission images causes inaccuracy in attenuation correction, since only one static attenuation map is used for each frame. For hardware motion tracking methods, head motion is assumed to be rigid, and the position of the head is monitored during the scan with devices such as the Polaris optical tracking tool¹⁰ or a structured light 3D tracking system.¹⁵ Motion data, which describe the six degree-of-freedom transformation of the head to a reference orientation, are recorded for postprocessing of the scan data. Herzog *et al.* reported noticeable reduction of motion artifacts in kinetic parameter estimates in real studies using the external tracked motion data and frame-based motion correction.⁴

When accurate externally tracked motion data are available, in theory, event-by-event motion correction has the potential for the greatest accuracy. We have implemented this approach in MOLAR, the Motion-compensation OSEM List-mode Algorithm for Resolution-recovery reconstruction for the HRRT,¹⁶ and routinely use this algorithm in human brain

PET reconstructions. In this study, we evaluated the accuracy of both event-by-event based and frame-based motion correction methods for a wide variety of motion profiles, taken from measured human motion data. Both static and dynamic simulated list-mode data with frame-based image reconstructions were used so that true activity values and the true parameters of the tracer kinetic models were known, in addition to perfect knowledge of the subject's motion. A potential measure was evaluated to assess the accuracy of motion correction in real studies, which lack a gold standard. In comparison to previous research in this area, our study quantified subject motion so that a numerical correlation between the motion artifact and the magnitude of motion can be drawn. In addition, the simulation studies with known ground truth enabled us to quantify the absolute bias in regional activities and tracer kinetic parameter estimates.

2. MATERIALS AND METHODS

2.A. Simulation of list-mode HRRT data

Both static (3D) and dynamic (4D) list-mode data were simulated as described below. The high-count 3D simulations were aimed at examining the effect of motion on the intensities of regions of interest (ROI). The 4D simulations were aimed at assessing the effect of motion on the accuracy of parameter estimates in tracer kinetic models.

2.A.1. Simulation of static list-mode HRRT data

Simulation of 3D static list-mode data was performed as follows: The “true image” for the simulation of radioactivity (λ , Bq/ml) was created from a static human brain PET image reconstructed using all the counts with event-by-event motion correction with corrections for randoms and scatter in a 120-min dynamic PET scan with [^{11}C]AFM, a ligand for the serotonin transporter.¹⁷ This radiotracer has high uptake in small brain regions such as the raphe nucleus, whose intensities are more likely to be affected by uncorrected motion (see Sec. 4 for details). The corresponding transmission image (μ) for this subject was used for simulating attenuation.

Each 120-min PET scan (bolus injection of 733 MBq of [^{11}C]AFM) was divided into 24 5-min frames. Within each simulated frame, the tracer distribution remains unchanged aside from motion, and the same tracer distribution was used for all frames. Each time frame of duration T (5 min) is divided into n_T (6000) sub-bins of duration Δt (1/20 s). A total of 5×10^8 M lines of response (LORs) out of the possible 4.5×10^9 HRRT LORs were sampled in a random spatial order for the entire duration of the frame. Since LORs are sampled randomly, the same LOR can appear multiple times in one frame, as is possible in real data. Within each Δt , the expected number of events for each of the 8.33×10^4 K (500 M/6000) uniquely selected LORs was computed with the forward projection model of MOLAR [Eq. (1)]:

$$E(Y_{i,t}) = \Delta t \left(\sum_j c_{i,t,j} L_{i,t} A_{i,t} N_i \lambda_j \right). \quad (1)$$

Here, $Y_{i,t}$ is the number of prompt coincidences in LOR i in time bin t . $L_{i,t}$ is the dimensionless product of decay factor at time t , lifetime factor (inverse of deadtime correction factor) at time t , and positron branching fraction. $A_{i,t}$ is the dimensionless attenuation factor. N_i is a sensitivity (normalization) factor, in units of (counts/s)/(Bq/ml mm), which converts the forward projection through the image grid λ (Bq/ml) to units of counts/s. $c_{i,t,j}$, defined in Eq. (2), is the system model (units of mm) that represents the contribution of voxel j to LOR i in time bin t , accounting for geometry, resolution, solid angle, and motion effects. This means that it should be updated whenever there is updated motion data.^{16,18–20} For this reason, $c_{i,t,j}$ is termed as the system model here instead of the classic system matrix to reflect the motion dependency:

$$c_{i,t,j} = f_{i,t}^r(\Delta r_{i,t,j}) f_{i,t}^z(\Delta z_{i,t,j}) \Omega_{i,t,j}. \quad (2)$$

Here, Δr and Δz are the perpendicular distance from the center of the voxel to the motion-corrected LOR in the radial and axial directions, respectively. $f_{i,t}^r(\Delta r)$ and $f_{i,t}^z(\Delta z)$ are the radial and axial components of the line spread function, which are Gaussian functions with 2.5 mm FWHM. $\Omega_{i,t,j}$ represents the solid angle term for the efficiency of the detection of events from voxel j in LOR i . Excluding the solid angle term, the same PSF was used to model the attenuation factor of each LOR.

The computed expected values were scaled up by a factor of 9 (4.5B/500 M) to account for the undersampling of the 4.5×10^9 total LORs, and finally list-mode data were created by simulating Poisson random variables with the determined expected values. In this work, the simulated list mode datasets accounted for detector resolution, normalization, and attenuation, but ignored random or scattered coincidences. Each static simulated frame required about 4 h of computation time on a computer cluster using 16 nodes.

2.A.2. Simulation of dynamic list-mode HRRT data

4D dynamic list-mode data were also simulated using the above mentioned physical model. In the dynamic simulation, 112 brain regions were defined from an automatic anatomical labeling (AAL) brain template.²¹ The frame timing was 6×30 s, 3×1 min, 2×2 min, and 22×5 min, following our standard approach. The 120-min time-activity data ($\lambda_{j,t}$) for each brain region were calculated with 0.1 s sampling interval using a 1-tissue compartment model using two tracers: [^{11}C]AFM (Ref. 17) and [^{11}C]PHNO (ligand for dopamine D₂/D₃ receptors).²² The input functions for the two tracers were measured from the arterial blood input taken from real studies, and the tracer uptake rate constant K_1 [ml/(min cm³)] and clearance rate constant k_2 (min⁻¹) were determined from the real study using the one-tissue compartment model.

2.B. Motion data

For each simulation, event-by-event motion data were included in the forward projection by transforming the end-points of each LOR i with the transformation matrix generated by the Vicra infrared motion tracking system (NDI, Waterloo,

Canada) from human data. Tracked human head motion data from over 500 PET studies were evaluated. The Vicra 3D infrared tracking system illuminates and tracks machined rigid body tools supporting reflective spheres in unique geometries. Multiple tools may be tracked simultaneously at 20 Hz. One tool was attached to a polyester fabric swimming cap worn by the subject. A second tool, the reference tool, was rigidly mounted on the PET scanner frame. A one-time calibration established the relationship between the scanner and reference tool coordinate systems. The reference tool approach allows straightforward calculation of head tool motion relative to the scanner image space and also makes this calculation independent of possible Vicra sensor motion or vibration. Vicra tracking data encode rotations as quaternions and include 3D translation vector. The quaternions are converted to transformation matrices for motion correction.

For each frame, the magnitude of intraframe motion of any point within the field-of-view (FOV) was determined as twice the standard deviation of motion of that point, as shown in Eq. (3). The rationale of this definition is given in Sec. 4.A. In order to describe the motion of the entire brain, eight points were selected as the vertices of a 10-cm cube centered in the scanner FOV, and the average motion of the eight points was determined as the intraframe motion:

$$m = \frac{1}{8} \sum_{p=1}^8 2 \times \sqrt{\sigma_{x_p}^2 + \sigma_{y_p}^2 + \sigma_{z_p}^2}. \quad (3)$$

Here, σ_{x_p} , σ_{y_p} , and σ_{z_p} are the standard deviations of the x , y , and z positions of point p in the brain over all motion data values within that frame. For each point, its transformed position is calculated using the motion transformation matrix at 20 Hz, and the standard deviations of the resulting x , y , and z values are calculated to be σ_x , σ_y , and σ_z .

In this work, ten large-motion datasets were selected from over 500 human brain scans. For each 2-h scan, the magnitude of motion M is defined as the average of the intraframe motions in each frame, weighted by the number of events within each frame. Figure 1 shows the distribution of M for the 500 scans evaluated. For the ten selected datasets, M ranged from 2.8 to 8.2 mm (5.7 ± 1.9 mm), which samples the largest 15% of motion. Large motions were chosen since they are more likely to introduce image artifacts and biases in the estimated parameters in tracer kinetic modeling. The static and the dynamic studies used the same motion data. To categorize motion in the static studies, the 240 5-min frames (10 studies, 24 frames each) in the static simulation were grouped into small (<5 mm), medium (5–10 mm), and large (>10 mm) intraframe motions. For these 240 frames, 15% have large motions and 26% have medium motions.

2.C. Image reconstruction

Images from individual frames were reconstructed with MOLAR, an OP-OSEM algorithm, as described in the fol-

FIG. 1. Distribution of the weighted average motion for over 500 scans with bin size of 1 mm. About 15% of the scans have >3 mm intraframe motion, which is the focus of this study.

lowing iteration equation:

$$\lambda_j^{(n+1)} = \frac{\lambda_j^n}{Q_j} \sum_{k=1}^k \frac{c_{l'_k, j} L_{l'_k} A_{l'_k} N_{l'_k}}{T \left(\sum_{j'} c_{l'_k, j} L_{l'_k} A_{l'_k} N_{l'_k} \lambda_{j'}^n \right)},$$

$$l'_k = \mathfrak{S}_k(l_k),$$

$$Q_j = \frac{1}{n_T} \sum_{t=1}^{n_T} \sum_{i=1}^I c_{i, t, j} L_{i, t} A_{i, t} N_i. \quad (4)$$

Here, l_k represents the k th detected LOR. $\mathfrak{S}_k$ is the transformation matrix that transforms the endpoint coordinates $[(x_{k, 1}, y_{k, 1}, z_{k, 1}), (x_{k, 2}, y_{k, 2}, z_{k, 2})]$ of LOR k , to a new LOR $l'_k[(x'_{k, 1}, y'_{k, 1}, z'_{k, 1}), (x'_{k, 2}, y'_{k, 2}, z'_{k, 2})]$. In other words, the LOR is mapped back to the reference position, defined as the average orientation of the head during the transmission scan. Therefore, motion correction maps each LOR back to where the head was during the transmission scan, thus correctly aligning the attenuation map to the emission scan. Note that the normalization factor (N) uses the original location of each LOR without motion correction, since it is based on the actual detector pair of each event.

In addition, Q_j is the voxel sensitivity term, in units of (count/s)/(Bq/ml), whose summations, in principle, occur over all LORs i over all time periods t in the time frame. In MOLAR, Q is approximated by a random and unique sampling of LORs for each reconstruction, to avoid the calculation for all possible LORs, while accounting for the unique motion in each frame by repositioning the randomly sampled LORs, as described above.¹⁶ Thus, the sensitivity image Q is calculated uniquely for each frame and incorporates the effect of motion. In this study, the number of randomized LORs used to compute Q , is roughly five times the number of the simulated true events in each frame in both static and dynamic studies (see Sec. 4).

The frame-based image reconstruction used 2 iterations and 30 subsets, with subsets defined based on the order of arrival of each event. The algorithm was initialized to a uniform

value except that voxel values (λ) outside the attenuation object ($\mu = 0$) were set to 0. The mask for the attenuation map was expanded by five voxels from the border to allow slight misalignment between the attenuation map and the emission image.

2.D. Motion correction methods

Four motion correction methods were compared in this study. As described below, EBE is the event-based motion correction method, and AVG, RBA, and RAA are different implementations of frame-based motion correction methods. All methods used the MOLAR software, so other aspects of the reconstruction were kept identical.

- **EBE**—Event-by-event list-mode based motion correction with known motion data, as described in Sec. 2.C. This is the best case scenario for motion correction since the list mode data were simulated with this exact motion.
- **AVG**—Motion correction using an average of the externally tracked motion data for each frame. The average motion data were obtained by taking the arithmetic average of the quaternion components of all the measured motion data within the frame. Only one set of motion information was used for each frame, and no postreconstruction image registration was performed.
- **RBA**—Frame-based motion correction using the motion information determined from registration of images before attenuation correction.²³ Images were first reconstructed *without* attenuation and motion correction, and were then registered to a reference image, which was reconstructed without attenuation correction from a motionless and noise-free simulation. Rigid body image registration was performed using the FLIRT software (<http://www.fmrib.ox.ac.uk/fsl/flirt>), based on normalized mutual information and included six degrees of freedom.^{7,24} This algorithm generates a transformation matrix that was then used as the motion data for this frame to re-reconstruct an image with attenuation and motion correction.
- **RAA**—Registration of images after attenuation correction. In this method, images were reconstructed with attenuation correction (but incorrectly aligned with the emission image due to motion), and were then registered to a noise-free reference frame that contains no motion in both the simulated list-mode data and the reconstruction process.

In summary, EBE, AVG, and RBA used different motion information during the reconstruction and RAA used no motion information during reconstruction. Postreconstruction registration was only performed for RAA. In addition, reconstruction with no motion correction (NMC) and reference motion-free simulation and reconstruction (REF) were also included in this work as negative and positive controls, respectively. The REF method was included to examine the bias and variance effects of the reconstruction algorithm without motion, since all list mode reconstructions are based on a finite number of events and are thus noisy.

2.E. Image analysis and parameter estimation

2.E.1. ROI intensity quantification

In the static study, ROI-based quantification was performed to evaluate the accuracy of each motion correction method. ROIs were defined based on reference to a MR template by first nonlinearly registering the MR image of the subject whose PET scan was the basis of the simulation to the ROI template that delineates the different brain structures, and then registering the PET image to the MR image of the subject. Both registrations were estimated by the FLIRT software (FSL, version 3.2),^{6,25,26} using the mutual information algorithm. MR imaging was performed on a 3T Trio (Siemens Medical Solutions, Erlangen, Germany) with a circularly polarized head coil. MR acquisition was a Sag 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence with 3.34 ms echo time, 2500 ms repetition time, 1100 ms inversion time, 7° flip angle, and 180 Hz/pixel bandwidth. In the dynamic studies, following our standard practice, the summed image from the first 10-min of data was registered to the subject's MR image, which had previously been registered to the ROI template. The ROIs evaluated here were midbrain raphe (0.6 cm³), thalamus (8.6 cm³), caudate (15.4 cm³), and anterior cingulate cortex (21.3 cm³), all of which have high [¹¹C]AFM uptake.¹⁷ The average ROI intensity within each of the above ROIs was calculated for all images, and bias was calculated as the percent difference with respect to the true image used in the simulation.

2.E.2. Statistical analysis

The *F*-test was used to determine if the bias in ROI intensities is correlated with the magnitude of motion for all motion correction methods. For each of the four ROIs, the percent bias in ROI intensity was linearly fitted against the magnitude of motion using a two-parameter linear model, $y = ax + b$. The *p*-value was calculated using the *F*-value and (1, 238) degrees of freedom for each ROI and for each motion correction method. If the *p*-value is less than the false-rejection probability (α) of 0.05, we reject the null hypothesis and conclude that the bias in intensity is dependent on the magnitude of motion.

2.E.3. Parameter estimation in tracer kinetic model

In the dynamic study, the TACs of each image pixel from all reconstructions were fitted to the one-tissue compartment model to estimate the uptake rate K_1 and clearance rate k_2 . A weighted least squares algorithm was used, with weights based on noise-equivalent counts. The parameter estimates of those voxels within each ROI are averaged to represent the kinetic parameters (K_1 and k_2) for that ROI. The same input function that was used in the simulation was used in the fitting. The volume of distribution V_T (K_1/k_2) and the binding potential BP_{ND} ($V_T/V_{T(\text{reference})} - 1$) of the high-uptake ROIs with true BP_{ND} greater than 1.0 (37 ROIs for [¹¹C]AFM and 10 ROIs for [¹¹C]PHNO) were computed on the parametric images and compared with the true values used in the simulation to assess the accuracy of each motion correction method.

2.E.4. Weighted residual sum of square difference between TACs

In the dynamic study, the noise-equivalent count-weighted residual sum of squared differences (WRSS) between the TAC and the fitted curve for the high-uptake ROIs were calculated and plotted as a function of motion magnitude. The purpose of this analysis is to investigate a potential figure-of-merit to assess the success of motion correction in real dynamic studies, which lack a gold standard.

3. RESULTS

3.A. Static study

3.A.1. Static images

Figure 2 shows the true image and the reconstructed images using the five different motion correction methods for a frame with large intraframe motion (14.8 mm) in the static study. In the transaxial view [Fig. 2(a)], only the EBE method

FIG. 2. Reconstructed images using each motion correction method in (a) transverse and (b) sagittal views. Images in each orientation are scaled to the respective maximal intensity in that view. The magnitude of the within-frame motion was 14.8 mm. See text for abbreviations. The EBE method reliably corrects for the motion and displays comparable ROI intensity as the true image. The ROIs denoted by the arrows are underestimated for the AVG, RBA, and RAA motion correction methods (a). Also, blurring is observed at the top edge of the brain for the AVG, RBA, and RAA method (b).

gives comparable voxel intensities as motion-free REF in the thalamus ROI, as denoted by the arrows. This high-uptake region shows reduced values for the AVG, RBA, and RAA methods. Also, in the sagittal view [Fig. 2(b)], observable image blurring is denoted by the ovals at the top edge of the brain for the AVG, RBA, and RAA methods. Since this is a single frame, blurring in AVG, RAA, RBA, and NMC images will be identical. Only the effect of attenuation mismatch will be different.

3.A.2. ROI quantification

Figure 3 shows the average image intensities within various ROIs as a percentage of the true values in the static study. The standard deviation bar represents the variation across simulations and reconstructions that used different motion data within the same motion category. ROIs of difference sizes, shapes, and locations within the brain are selected to examine the effect of motion on different brain regions. Across the four ROIs shown in Fig. 3, the EBE motion correction method gives comparable ($99.2\% \pm 1.9\%$) normalized ROI intensities to the no-motion reference case ($98.6\% \pm 1.0\%$), regardless of the magnitude of the motion. The standard deviation here represents the variation across the four ROIs. The differences among all the motion correction methods are subtle when the intraframe motion is small (less than 5 mm). For medium motions between 5 and 10 mm, the ratios of ROI intensities to the true values are $94.9\% \pm 2.8\%$ and $95.0\% \pm 2.7\%$ for AVG and RBA, respectively. For large motions (>10 mm), the intensity ratios drop to $90.1\% \pm 5.9\%$ and $90.7\% \pm 5.3\%$, respectively. The RAA method shows a greater drop in the average ROI intensities than the other motion correction methods across all ROIs, due to both the misalignment between the subject and the attenuation map as well as interpolation smoothing in the postprocessing. For medium (5–10 mm) and large (>10 mm) motions, the average ratios of the ROI intensities to the true values for RAA are $92.8\% \pm 5.3\%$ and $88.3\% \pm 6.7\%$, respectively.

3.A.3. Statistical analysis

The magnitude of quantification error was compared to the magnitude of intraframe motion using the F test. For EBE, the p -values for each of the four ROIs were not significant (0.53, 0.39, 0.14, and 0.92). On the contrary, for all non-EBE motion correction methods, the p -values were less than 0.01 for all ROIs, indicating that the bias in ROI intensity is linearly dependent on the magnitude of motion for the frame-based motion correction methods.

The slopes a in the linear model $y = ax + b$ are shown in Table I for each ROI. Here, the physical meaning of the slope is the percent reduction in ROI intensity per mm of motion. As shown in Table I, the slopes for AVG, RBA, and RAA ranged between -0.41 and -0.99 for the four ROIs, indicating a bias of $\sim 0.4\%$ – 1% per mm, which is noticeably larger than EBE (0 – 0.03), suggesting motion-dependent bias in ROI intensity for the frame-based motion correction methods. The

FIG. 3. The ratio of ROI intensities to those of the true image in the static analysis as a function of the magnitude of intraframe motion, using each motion correction method. Four ROIs, (a) midbrain raphe (0.6 cm^3), (b) thalamus (8.6 cm^3), (c) caudate (15.4 cm^3), and (d) anterior cingulate (21.3 cm^3), with various sizes and locations within the brain are shown. When motion is small ($<5 \text{ mm}$), the discrepancies in ROI intensities from the true image are subtle for all motion correction methods. For medium ($5\text{--}10 \text{ mm}$) and large ($>10 \text{ mm}$) intraframe motions, the ROI intensities are $\sim 5\%$ and 10% lower than the true values, respectively, for the AVG, RBA, and RAA methods. In contrast, the EBE method reliably corrects for motion of all magnitudes and yields ROI intensities that are close to the true values and comparable to the reference (REF) no-motion case.

y-intercepts of the linear fit were very close to zero, with most noticeable intercepts of 1% – 6% in the case of RAA.

3.B. Dynamic study

3.B.1. Parametric images

The estimated values of V_T for each image pixel for the two tracers in a study with 7.8 mm weighted average motion are shown in Fig. 4. For $[^{11}\text{C}]\text{AFM}$ [Fig. 4(a)], the high-uptake thalamus ROI is denoted by the arrows. Compared to the true

V_T image used in the simulation (TRUE), both the no-motion reference (REF) and EBE are able to recover the shape and intensity level of the thalamus ROI. The frame-based motion correction methods AVG, RBA, and RAA show some degree of reduction in the ROI intensity in the thalamus. For $[^{11}\text{C}]\text{PHNO}$ [Fig. 4(b)], the substantia nigra ROI is marked by the arrows. Compared with the true V_T image used in the simulation (TRUE), the no-motion reference (REF), and event-by-event motion correction (EBE) gave comparable ROI intensities, whereas some degree of blurring of the substantia nigra is observed in each of the frame-based motion correction methods AVG, RBA, and RAA.

TABLE I. Slopes of the linear fit. The slopes represent the percent reduction in ROI intensity per mm of motion.

ROI	EBE	AVG	RBA	RAA
Raphe	−0.03	−0.59	−0.56	−0.42
Thalamus	−0.02	−0.55	−0.55	−0.41
Caudate	0.00	−0.99	−0.93	−0.97
Anterior cingulum	−0.03	−0.61	−0.55	−0.63

3.B.2. Parameter estimates

Figure 5 shows the ratio of the estimated V_T [Figs. 5(a) and 5(b)] and BP_{ND} [Figs. 5(c) and 5(d)] to the true values for the high-uptake ROIs ($BP_{ND} > 1.0$) for $[^{11}\text{C}]\text{AFM}$ [Figs. 5(a) and 5(c)] and $[^{11}\text{C}]\text{PHNO}$ [Figs. 5(b) and 5(d)], respectively. A total of 37 high-uptake ROIs were included for $[^{11}\text{C}]\text{AFM}$, and 10 for $[^{11}\text{C}]\text{PHNO}$. Across all motions, the EBE method gave

FIG. 4. Distribution volume (V_T) image of $[^{11}\text{C}]\text{AFM}$ (a) and $[^{11}\text{C}]\text{PHNO}$ (b). The high-uptake ROIs thalamus (a) and substantia nigra (b) are denoted by the arrows. The no-motion reference (REF) and the EBE motion correction give comparable ROI shape and intensity to the true V_T image used in the simulation (TRUE). The frame-based methods AVG, RBA, and RAA show some level of reduction in the ROI intensity. With NMC, substantial blurring is observed.

comparable estimates of V_T and BP_{ND} to the motion-free case, whereas the frame-based methods introduced sizeable negative bias for large motions. As the weighted-average motion exceeds 5 mm, approximately 5% bias in V_T and 10% bias in BP_{ND} are observed for the frame-based motion correction methods. Comparable results are seen for AVG and RBA, suggesting that these two frame-based motion correction methods behave similarly in high-count frames. However, AVG is expected to be superior to RBA for low-count frames, due to the potential inaccuracy in software-based image registration of noisy images.

3.B.3. WRSS between raw TAC and fitted curve

Figure 6 shows the WRSS between the raw TAC and the fitted curve for $[^{11}\text{C}]\text{AFM}$ [Fig. 6(a)] and $[^{11}\text{C}]\text{PHNO}$ [Fig. 6(b)] for each motion correction method, normalized to the WRSS of the no-motion reference. The normalized WRSS (nWRSS) for the high-uptake ROIs were averaged. A value of 1 for normalized nWRSS is the perfect scenario, in which the motion-corrected reconstruction shows the same WRSS as the motion-free case. For event-by-event motion correction, WRSS is close to 1 across all motions. For the frame-based

motion correction methods (AVG, RBA, and RAA), nWRSS rises to 2–4 as the magnitude of motion grows. This suggests that WRSS might be useful to assess motion correction if a suitable normalization can be chosen.

4. DISCUSSION

The simulations in this study examined the effect of intraframe motion on quantification errors in PET and compared different motion correction methods. These simulations were performed with actual human head motion data, where preferentially large motions were examined to characterize the potential errors. In addition, the simulation used true brain emission distributions with high- and low-uptake regions to characterize the effects. The study showed that considerable errors are introduced when the weighted average intraframe motion exceeds 5 mm. While previous studies similarly demonstrated motion-induced increased bias and variability in ROI intensities and tracer kinetic parameter estimates,^{4,27} our simulation-based study examined the absolute biases from the ground truth, and explored the correlation between the biases and the magnitude of motion. Strictly, to perform the simulation with motion in an ideal fashion

FIG. 5. Ratio of kinetic parameter estimates of [^{11}C]AFM (a) and (c) and [^{11}C]PHNO (b) and (d) to the true values for each motion correction method. The high-uptake ROIs with $BP_{ND} > 1.0$ (37 ROIs for [^{11}C]AFM and 10 for [^{11}C]PHNO). Volumes of distribution (V_T) values are shown in (a) and (b), and binding potential (BP_{ND}) values are shown in (c) and (d). EBE gives comparable V_T and BP_{ND} estimates to motion-free, whereas the frame-based methods show $\sim 5\%$ bias in V_T and $\sim 10\%$ bias in BP_{ND} as the weighted average intraframe motion exceeds 5 mm.

would require determining the expected value of 4.5×10^9 HRRT LORs 6000 times for each 5-min frame (once per Vira measurement), which would have been a computationally intractable approach. Alternatively, Monte Carlo simulation would have given a more precise simulation model that includes all physics terms. However, it would have been even more computationally intensive. Further, by using the same physics model for the simulation and the reconstruction, as done here, all errors can be attributed to insufficiencies in motion correction, instead of discrepancies between Monte Carlo and the reconstruction data model.

4.A. Quantification of motion

In this study, we summarized the motions with a single value, defined in Eq. (3). This definition is based on the idea that if an object stays at one spot for half the duration of a frame, and moves to another spot at a distance d away from the first spot for the rest of the frame, the magnitude of motion for this frame will be $m = d$. It is worth noting that if

the object moves at a constant speed for a distance d from the beginning to the end of the frame, the motion magnitude will be $m = d/\sqrt{3}$ by this definition. The magnitude of motion for this case is around half of the magnitude for step motion, which is reasonable as the effect of continuous motion will be smaller than step motion. This definition of motion magnitude incorporates both rotational and translational components in the motion measurement, and the magnitude of motion is quantified by one value so that motion can be conveniently categorized based on its magnitude. This definition differs from previous reported methods^{27–29} in which motion data were reported based on separate translational and rotational components of the motion transformation matrices.

4.B. Comparison of the motion correction methods

Each of the registration-based motion correction methods, i.e., RBA and RAA, has potential drawbacks. For RAA, the attenuation map is misaligned with the object, thus creating errors in attenuation and scatter correction. The RBA method

FIG. 6. Normalized WRSS (nWRSS) between the raw TACs and the fitted curves as a function of motion for $[^{11}\text{C}]\text{AFM}$ (a) and $[^{11}\text{C}]\text{PHNO}$ (b). The event-by-event motion correction gives comparable WRSS to the motion-free data ($\text{nWRSS} = 1$) for all motions, whereas the frame-based motion corrections show nWRSS values of 2–4 when the weighted intraframe motion gets large.

solves this issue through two reconstructions. The images were first reconstructed without attenuation correction, and were then registered to another emission image without attenuation correction in the reference orientation. The second reconstruction included an attenuation map that was resliced to the average orientation of the object during the emission frame. In the evaluation of RBA performed here, the reference emission image used for registration was perfect, i.e., it was produced without motion. In real studies, such an ideal reference emission image does not exist, so any reference image might be in error due to intraframe motion. Since reference images are often chosen to have high statistics, thus with long duration, intraframe motion is likely. In addition, in the static simulations, the emission distribution is not changing, so the PET-to-PET registration is likely to produce minimal error. In the real world, as demonstrated in the dynamic simulation, the distribution of radiotracer changes with time across frames, thus reducing the reliability of interframe registration.

In contrast, the EBE and AVG methods use motion data from the external tracking device, thus eliminating the necessity of image registrations. These methods rely on accurately

measured motion data during the scans. The Vicra hardware-based motion tracking involves attaching reflective markers to a tool affixed to a swimming cap that is worn by the subjects. Occasional slipping of the swimming cap has been observed by us and by Dinelle *et al.*³⁰ Currently, our strategy is to wrap the tool with COBAN wrap, which tightly affix the swimming cap on the head, and to hopefully eliminate any wobbling motion of the marker or slip of the swimming cap. A more ideal solution would be an accurate motion-tracking device that does not require attaching a tool to the subject's head.¹⁵

The AVG method uses the average of the externally tracked motion data within each frame. The accuracy of averaging transformation matrices for large motion deserves some attention. In our approach, we averaged the rotational components of the transformation by calculating the mean of the quaternions, and calculated the mean of the translational components. An alternative is to estimate the average transformation matrix using Karcher's weighted-mean transformation.³¹

The large difference between RAA and NMC is due to progressive motion during the 2-h scan. For NMC, no frame-by-frame registration is performed; only registration of the 0–10 min average image to the subject's MR is performed for ROI definition. As each scan is divided into twenty-four 5-min frames, the later frames are also affected by the accumulative motion. We investigated the correlation between the average of the 5-min intraframe motions and the magnitude of motion during the entire 2-h scan. We found that $M_{\text{scan}} = 3.3M_{\text{intraframe}} + 2.7$ mm. The correlation coefficient between M_{scan} and $M_{\text{intraframe}}$ is ~ 0.6 . This suggests that the effect of interframe motion substantially contributes to the bias in NMC as compared to RAA.

4.C. ROI-dependence of motion

The magnitude of motion at different positions in the FOV is variable, due to the nature of head motion about its pivot point at the back of the head, and the distance of a given spot from this point. Typically, the center of the brain moves less than the anterior portions and more than the posterior positions. To account for the variation in the magnitude of motion, we chose eight spots in the FOV to compute motion and average the motion magnitudes of these positions. In this study, most of the high-uptake brain regions for the tracer $[^{11}\text{C}]\text{AFM}$ are located in the center of the brain, thus their variation in the magnitude of motion is minimal.

The size and the shape of the ROIs also determine how much effect uncorrected motion has on ROI intensity. Small ROIs are expected to be more significantly affected by motion than large ROIs, as the smoothing effect of motion primarily only reduces the intensity of the image voxels at the edge of the ROIs. This renders small ROIs with large surface areas more vulnerable to motion than large spherical ROIs. However, in this study, the drop in ROI intensity is comparable regardless of the size of the ROI, which is likely due to the fact that some small ROIs with high uptake of the $[^{11}\text{C}]\text{AFM}$ are located close to each other, and motion may move the neighboring high-uptake voxels into the ROI that we investigate.

This effect can be observed in Fig. 3. The midbrain raphe (0.6 cm^3) is much smaller and has higher uptake than the caudate (15.4 cm^3), thus its intensity would be expected to be more substantially affected by motion than the caudate. However, similar degradation due to motion is observed for these two ROIs (Fig. 3), due to the fact that other high-intensity regions are near the midbrain raphe, so that certain motion moves activity into the location of midbrain raphe ROI, thus reducing the motion-induced bias. For the anterior cingulate, the bias in ROI intensity for NMC is smaller than the other ROIs, perhaps because this region is the largest among the four that were investigated in Fig. 3. Also, the local contrast for the anterior cingulate is lower than that of other ROIs, thus reducing the effect of motion.

4.D. Accuracy of motion correction in real studies

Here, the WRSS has been evaluated as potential figure-of-merit to assess the accuracy of motion correction in real dynamic brain PET studies. However, in real studies, there is no true motion-free image for normalization of the WRSS figure of merit. A solution is to estimate the theoretical variance of the image pixel intensities, and thus a motion-free WRSS between the raw TAC and fitted curve may be estimated for each compound. It should be noted that not all tracer kinetic models give good fits to the raw TACs, and a lack-of-fit scenario may reduce the utility of the nWRSS to assess the accuracy of motion correction.

4.E. Effects of frame duration on motion

It is clear that shorter frames contain less intraframe motion than longer frames. Therefore, strategically dividing the frames based on measured motion data can effectively minimize intraframe motion. This approach has been developed in human¹³ and animal³² studies. The aim of this work is to investigate the effects of the magnitude of intraframe motion on the accuracy of image intensities and tracer kinetic parameter. In this work, we observed that the AVG and RBA methods give comparable results, suggesting that image registration may work as well as having true motion information for high-count frames. However, shorter frames introduce higher noise level in the images, which may generate inaccurate software-based image registration. In addition, reducing the frame durations may introduce bias in ROI intensities for OSEM-based reconstruction.^{33,34}

4.F. Effects of random and scattered events on motion correction

The simulation of list-mode data and the reconstructions performed here excluded randoms and scattered events. Randoms and scattered events must be handled appropriately in motion correction, as reported by Rahmim *et al.*³⁵ Random events tend to be uniformly distributed in the FOV, and the effect of uncorrected motion on randoms correction is likely insignificant. In MOLAR, the estimated randoms count rate for each event is determined from the singles rates of the two

detectors for that event, thus correction for randoms in this manner is not sensitive to motion.

Motion affects the accuracy of scatter correction in a more complex way. The MOLAR algorithm uses the single scatter simulation method³⁶ to first simulate the scatter distribution in the entire FOV and then scale this distribution based on the number of counts (prompts minus delays) outside the edge of the object. Two types of errors may result from motion. First, uncorrected motion shifts the emission image away from the attenuation map of the subject. The misalignment between the emission and attenuation images results in inaccurate estimation of the scatter distribution. Also, when scaling the simulated scatter distribution by the number of events outside of the object, the misalignment between the emission image and the attenuation map shifts counts that are within the object outside the edge of the subject, creating an incorrect estimate of the scattered events outside the subject, and thus the wrong scatter scaling factor. In the presence of motion, the exact orientation of the detectors with respect to the scattered LOR should also be determined to account for altered photon angles of incidence relative to the detectors. Thus, in principle, the scatter calculation would be repeated for each subject position. This is clearly too computationally expensive, so, for the purpose of scatter estimation, the MOLAR algorithm uses the average motion data within each frame to transform the coordinates of the detectors. Thielemans reported a scatter estimation method in the presence of motion.³⁷ In this method, the scatter is estimated for a reference relative position between the object and the scanner. Motion data are used to transform the scatter estimate in the presence of motion. If scatter had been included in this work, we would have expected to see some fluctuation in the estimated scatter fraction, depending on the amount of motion within a frame. However, this variation in scatter fraction is expected to be comparable across different motion correction methods, except perhaps for RAA, since the average of motion data is used to approximate motion in scatter correction for all methods.

4.G. Notable features of the MOLAR algorithm

One unique feature of MOLAR is the algorithm for calculation of the image sensitivity term, Q . As shown in Eq. (4), the computation of Q ideally incorporates motion by calculating the system model, $c_{i,t,j}$ for all LORs. Therefore, the voxel sensitivity image incorporates the effect of motion. Ideally, all of the 4.5×10^9 LORs of the HRRT should be used to calculate Q , which becomes computationally intractable to account for all LORs in all positions of the object. In practice, a random sampling of the 4.5×10^9 LORs is performed, and the final image sensitivity values are scaled to correct for the undersampling. This sampling approach can add noise to the reconstructed image if too few LORs are sampled in calculating Q . In practice, the number of LORs used in Q is set equal to the total number of events in each frame. In the static study, 5×10^8 M LORs were used in the Q calculation with 1×10^8 M events in each frame, a ratio that is five times higher than the standard setting to minimize noise in the

FIG. 7. The coordinates of the detected event L_k are $(x_{k,1}, y_{k,1}, z_{k,1})$ and $(x_{k,2}, y_{k,2}, z_{k,2})$ (a). After motion correction, the coordinates of the event are transformed to $(x'_{k,1}, y'_{k,1}, z'_{k,1})$ and $(x_{k,2}, y_{k,2}, z_{k,2})$ (b). In this example, $(x'_{k,1}, y'_{k,1}, z'_{k,1})$ does not correspond to a detector pair and the transformed LOR does not belong to any bin in sinogram space. As a result, the transformed LOR is excluded by sinogram-based methods. In contrast, MOLAR updates and keeps the coordinates of the motion-corrected event, and is able to use that event for reconstruction, improving statistics over sinogram-based methods.

image introduced by the Q calculation. The effect of incorporating motion in the subset of LORs to calculate a frame-specific Q was examined in the comparison between EBE and REF, since there is no motion in Q for REF. The close agreement between EBE and REF suggests that using a subset of randomized LORs to compute Q in the presence of motion does not introduce inaccuracies in the quantitative analyses.

In MOLAR, the location of each LOR is represented by the Cartesian coordinates of the LOR end-points without binning into sinograms.^{29,38,39} When event-by-event motion correction is performed, the coordinates are transformed by motion data from detector space into a fixed object-based space, which better preserves the accuracy of the location of each LOR than the sinogram rebinning technique, since the motion corrected event may not fall exactly on the center of detector crystals.

All motion-corrected LORs are used for MOLAR reconstruction, including those LORs that do not intersect with any detector pairs after motion correction [Fig. 7]. Such events are discarded in sinogram-based methods, as they cannot be assigned to any bin in the sinogram space, unless a user-defined sinogram that covers a larger FOV with additional oblique angles is used in the reconstruction.

In MOLAR, attenuation correction is incorporated in the calculation of the motion-dependent system sensitivity matrix, thus preserving the Poisson nature of the detected events. This approach differs from that of Rahmim *et al.*,¹⁹ in which counts are precorrected for attenuation, so that the system model is independent of attenuation. This latter approach produces higher computation efficiency at the possible price of increased image noise.

5. CONCLUSION

In this study, the accuracy of event-by-event and frame-based motion correction methods in brain PET imaging was evaluated using static and dynamic simulated PET list-mode data. The effects of motion on ROI intensities in the reconstructed images and on the parameter estimates in tracer kinetic models were examined as a function of the magnitude

of intraframe motion. We found that frame-based motion correction methods using motion data derived from image registration and using the average of externally tracked motion data give comparable quantitative accuracy for a wide range of human head motion. However, notable motion-induced biases in ROI intensity and tracer kinetic model parameters were observed when intraframe motion exceeds 5 mm. If accurate motion data are available, event-by-event motion correction can reliably correct for head motion. For small intraframe motion of less than 5 mm, the frame-based methods with correctly aligned attenuation map are also considered as reliable techniques for motion correction.

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