Accuracy and precision of zero-echo-time, single- and multi-atlas attenuation correction for dynamic [11C]PE2I PET-MR brain imaging

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Abstract

Background: A valid photon attenuation correction (AC) method is instrumental for obtaining quantitatively correct PET images. Integrated PET/MR systems provide no direct information on attenuation, and novel methods for MR-based AC (MRAC) are still under investigation. Evaluations of various AC methods have mainly focused on static brain PET acquisitions. In this study we determined the validity of three MRAC methods in a dynamic PET/MR study of the brain.

Methods: Nine participants underwent dynamic brain PET/MR scanning using the dopamine transporter radioligand $[^{11}\text{C}]$PE2I. Three MRAC methods were evaluated: single-atlas (Atlas), multi-atlas (MaxProb) and zero-echo-time (ZTE). The $^{68}$Ge-transmission data from a previous stand-alone PET scan was used as reference method. Parametric relative delivery ($R_1$) images and binding potential ($BP_{ND}$) maps were generated using cerebellar grey matter as reference region. Evaluation was based on bias in MRAC maps, accuracy and precision of $[^{11}\text{C}]$PE2I $BP_{ND}$ and $R_1$ estimates, and $[^{11}\text{C}]$PE2I time-activity curves. $BP_{ND}$ was examined for striatal regions and $R_1$ in clusters of regions across the brain.

Results: For $BP_{ND}$, ZTE-MRAC showed the highest accuracy (bias < 2%). Atlas-MRAC exhibited a significant bias in caudate nucleus (-12%) while MaxProb-MRAC revealed a substantial, non-significant bias in putamen (9%). $R_1$ estimates had a marginal bias for all MRAC methods (-1.0-3.2%). MaxProb-MRAC showed the largest intersubject variability for both $R_1$ and $BP_{ND}$. Standardized uptake values (SUV) of striatal regions displayed the strongest average bias for ZTE-MRAC ($\sim 10\%$), although constant over time and with the smallest inter-subject variability. Atlas-MRAC had highest variation in bias over time (+10 to -10%), followed by MaxProb-MRAC (+ 5 to -5%), but MaxProb showed the lowest mean bias. For cerebellum, MaxProb-MRAC showed highest variability while bias was constant over time for Atlas- and ZTE-MRAC.

Conclusions: Both Maxprob and ZTE-MRAC performed better than Atlas-MRAC when using a $^{68}$Ge transmission scan as reference method. Overall, ZTE-MRAC showed the highest precision and accuracy in outcome parameters of dynamic $[^{11}\text{C}]$PE2I PET analysis with use of kinetic modelling.

Introduction

In positron emission tomography (PET), a photon attenuation correction (AC) method is a prerequisite for obtaining dependable images and quantifications. Photon attenuation is the largest correction required in PET imaging as photon attenuation is inhomogeneous across tissues [1]. The amount of photon attenuation depends on spatially varying electron density as well as type of tissue and its thickness. PET AC routines therefore require knowledge about the spatial distribution of attenuation coefficients within the field of view (FOV) of the scanner, represented as an attenuation map whose voxel values denote linear attenuation coefficients [2–4].
Stand-alone PET systems include transmission scanning units, where photon sources are rotated around the subject and detectors record transmitted photons on the opposing side. Suitable sources are radionuclides (e.g. $^{68}$Ge/$^{68}$Ga) that emit photons with energies of 511 keV [5, 6]. This method is usually regarded as the gold standard for AC [7] as it measures 511 keV photon attenuation directly. In PET/computed tomography (CT) systems, AC is based on a low-dose CT scanning; this generates equivalent maps because the attenuation of X-rays transmitted through a specimen is directly correlated with electron density [8]. X-ray photons have lower energy (80–140 keV) and thus higher attenuation, so the CT data must then be converted from Hounsfield units to linear attenuation coefficients to obtain a suitable AC map for PET correction [9].

Integrated PET/magnetic resonance imaging (MRI) systems offer new opportunities and challenges. Neurological disorders are key applications with a long clinical tradition of combining functional information from nuclear medicine images with structural information from magnetic resonance imaging (MRI) to allow adequate quantifications across the brain. However, MRI provides no direct information on electron density that can be used for AC [10, 11]. Instead, MRI can supply proton density, but its correlation with gamma photon attenuation is highly nonlinear: bone, in particular, has low proton density and high electron density [12, 13]. Additional efforts are needed to determine which AC method can be implemented as a routine in an image reconstruction process.

Several approaches have been reported for MR-based attenuation correction (MRAC) of PET brain data. Initially, a Dixon-based approach was implemented for PET MRAC. This method is based on segmentation into tissue classes (i.e., air, lung, fat and soft tissue) to which linear attenuation coefficients are assigned [14, 15]. As the Dixon-based approach is primarily intended for whole-body PET-MR, the skull is not considered. As a consequence, this MRAC method is a source of a substantial bias in brain studies, especially for cortical regions [16–18]. In parallel, various atlas-based MRAC approaches were developed and evaluated. In this broad class of methods a single CT atlas [19], multiple atlases [20, 21] or a pair of MR model and skull mask [22] are applied to incorporate bone in the MRAC map. As no direct relationship exists between MRI and CT [23], various statistical methods have been applied to convert MR intensities to a pseudo-CT with Hounsfield units for discrimination of soft tissue, air and bone [23]. Generally, atlas-based MRAC methods improve accuracy by including the skull and seem to perform within acceptable quantitative limits [11, 24]. Most recently, segmentation of a zero-echo-time (ZTE) MRI sequence [12, 25] has been suggested for MRAC. With some resemblance to ultrashort-echo-time (UTE) sequence [26], ZTE was designed to obtain signal from cortical bone with both lower acoustic noise and reduced sensitivity to gradient fidelity artefacts [27]. As such, ZTE could be used to incorporate bone in a MRAC map, creating a solid basis for accurate soft tissue segmentation [10, 12, 25]. Several clinical evaluations demonstrated for static PET-data acquisitions that ZTE-based MRAC accomplished quantification with smaller errors than a single-atlas approach, both with CT AC [10, 28–31] or $^{68}$Ge AC as reference [32].

Until now, evaluations of various MRAC methods have mainly focused on static brain PET, showing merely the tracer uptake or target-to-reference ratios. In an independent multi-centre study where eleven MRAC methods were applied to a large cohort data set of static FDG PET/MR data, the average
performance in PET tracer uptake was generally within ± 5% of CT-AC [24]. However, dynamic brain PET holds the compelling promise of in vivo functional imaging, i.e. following physiological processes over time, or obtaining quantitative measures by means of tracer kinetic modelling. Several recent studies have reported results for dynamic PET data using various scanners, MRAC methods and radiotracers as well as different kinetic modelling approaches depending on the tracer kinetics [33–37]. In contrast to the static data [24] no comparative studies with standardized conditions have been conducted, and this prevents fair comparisons between studies. However, the majority of newly developed MRAC methods are based on segmentation or on an atlas [24]. Therefore, the multi-atlas approach (MaxProb) developed by Merida et al. [33] was included in the current study. MaxProb MRAC builds on a database of brain MR/CT image pairs and an application of a novel maximum-probability method [33]. A clinical application on static [18F]FDG PET/MR data demonstrated that MaxProb was highly accurate, with results equivalent to data reconstructed with CT-AC. MaxProb was also among the best performing methods in the comparative study on static PET/MR data by Ladefoged et al. [24]. In a dynamic setting with the serotonergic 1a tracer [18F]MPPF, an acceptable amount of bias in the estimated binding potential (BPND), ranging from −2.5 to 5.0%, was seen [33].

In this study we used 11C-labelled PE2I (N-(3-iodoprop-2E-enyl)-2β-carbomethoxy-3β-(4-methyl-phenyl) nortropane), a radiotracer with high affinity to dopamine transporters (DAT), especially in striatum [38]. Kinetic modelling of dynamic [11C]PE2I imaging data is able to determine both BPND, proportional to DAT availability, and relative delivery (R1) reflecting relative cerebral blood flow, from one single brain scan [39, 40]. These quantitative outcome measures are particularly important for the differential diagnosis in patients with parkinsonism [41], and used in clinical routine at our centre. Despite the promising evaluation reports of novel MRAC methods, it is still unclear how these approaches might perform in a dynamic dataset with a specific dopamine tracer and use of a kinetic modelling approach.

The aim of this study was to determine the validity of three different MRAC methods in a setting with a dynamic [11C]PE2I PET brain scan on a PET-MR system, using 68Ge-transmission AC as a reference method. We evaluated (1) a single-atlas method (Atlas-MRAC) [11], (2) an MR sequence-based method (ZTE-MRAC) [12, 25] and (3) a multiple-atlas method (MaxProb-MRAC) [33, 42] in a dynamic [11C]PE2I PET dataset acquired on an integrated digital time-of-flight PET-MR system. Individual transmission scans acquired on a stand-alone PET system were used as the reference method (68Ge-MRAC), directly measuring attenuation at 511 keV.

Methods

Participants and data acquisition

The participants and data acquisition have previously been described [32]. This study was approved by the Regional Board of Medical Ethics in Uppsala as well as the Radiation Ethics Committee of Uppsala University Hospital, and all participants consented in writing to take part in the study before inclusion.
The study comprised nine patients with Parkinsonism (5 females, 4 males; median age 72 years, range 49–82). Previously, each participant had undergone a 10 min transmission scan using three rotating $^{68}$Ge rod sources on an ECAT Exact HR + scanner (Siemens, Knoxville), prior to injection of any radioactivity. Participants then underwent a dynamic brain PET scan using $^{11}$C-PE2I on a 3T time-of-flight PET/MR (Signa PET/MR, GE Healthcare, Waukesha) system.

An 80-min PET scan was acquired in listmode, starting simultaneously with intravenous bolus administration of 5 MBq/kg $[^{11}\text{C}]$PE2I using an infusion pump, and divided into 22 time frames of increasing duration (4 × 60 s, 2 × 120 s, 4 × 180 s, 12 × 300 s). Relevant MR sequences were acquired during the first five minutes of the $[^{11}\text{C}]$PE2I PET scan to avoid misalignment due to head movements. Three MR sequences were acquired during the $[^{11}\text{C}]$PE2I PET scan: 1) a T1w 3D LAVA Flex that was later used for Atlas MRAC (duration 18 s, 1 NEX, FOV 500 mm, slice thickness 5.2 mm, matrix 256 × 256, and 5° flip angle); 2) a proton-density ZTE sequence (duration 153 s, 4 NEX, FOV 260 mm, slice thickness 1.4 mm, no slice gap, matrix 192 × 192, flip angle 0.8°) 3), and a 3D T1w brain volume imaging sequence – these images were later used for definition of regions of interest and as the target for MaxProb-MRAC registration (duration 272 s, NEX, FOV 250 mm, slice thickness 1 mm, matrix 256 × 256, flip angle 12°).

**Generation of MR attenuation correction maps**

For each participant, the following MR attenuation correction maps (MRAC) were produced:

*Atlas-MRAC* – The single-atlas based method [11] consisted of three steps: (1) application of a Hessian matrix to enhance bone structures in the T1w image, (2) pseudo-CT generation by registration of the enhanced image to a head atlas based on CT scans of 50 participants, (3) standard energy conversion and resampling of the pseudo-CT, resulting in an AC map with dimensions of 128 × 128 × 89 voxels (4.68 × 4.68 × 2.78 mm). This method was vendor-provided (software version MP26) as a standard application for our PET/MR system when the study was initiated.

*ZTE-MRAC* – In this procedure, an intensity equalization to a ZTE image was followed by logarithmic image rescaling to enhance bone tissue. Next, a mask was used to isolate the brain data, thus removing bed and coil information. A sequence of thresholding operations was then applied to the subject’s brain image to segment bone and air regions by fitting a Gaussian to the main image histogram peaks. Remaining internal air compartments were further segmented by means of histogram thresholding. Finally, the resulting MRAC image was co-registered and resampled to the subjects’ individual Atlas-MRAC by applying 6-parameter rigid-body registration creating the ZTE-MRAC map. This method is also a vendor-implemented process (GE PET Reconstruction Toolbox MP26), but during data acquisition still under development [12, 25].

*MaxProb-MRAC* – This method utilized a database of 40 corresponding MR and CT images [33, 42]. Processing steps were executed using an in-house MATLAB pipeline (MATLAB R2017a, Mathworks Inc., Natick, MA). Each MR image from the database was paired with the participant’s high-resolution T1w image and masking was applied to both images to reduce extraneous image information. In the following
registration steps, the masked MR-image pair was aligned by means of affine registration followed by non-rigid registration using normalized mutual information as the similarity measure (register github.com/BioMedIA/MIRTK). Subsequently, the transformation matrices acquired from the non-rigid registration of MR-images were applied to the corresponding CT images, yielding a database of co-registered MR/CT image pairs. In the next step, the co-registered CTs were segmented into three tissue classes defined by intensity thresholds (air: < -500 HU, soft tissue: -500-300 HU, bone: > 300 HU [19]. Each voxel tissue class of the target subject space was then assigned to a tissue class by majority voting of tissue class labels across the registered CT database. Finally, a voxel-wise pseudo-CT was generated by averaging CT Hounsfield values of atlases belonging to the majority class for the corresponding voxel. Similar to Atlas-MRAC, standard energy conversion was performed as the last step of attenuation map computation. The resulting MRAC image was rigidly co-registered and resampled to the participant's individual Atlas-MRAC. Thereafter, the MaxProb-MRAC image was completed by adding, from the Atlas-MRAC map, the neck information missing due to differences in axial FOV between the images retrieved from the MR/CT database (216 mm) and the PET/MR scanner (250 mm).

\[ ^{68} \text{Ge-MRAC} \] – Attenuation maps were reconstructed from the \[ ^{68} \text{Ge} \] transmission scan using ordered subset expectation maximisation (OSEM) with 6 iterations, 8 subsets and a 4 mm Hanning post filter, dimensions \( 128 \times 128 \times 63 \) voxels \( (5.15 \times 5.15 \times 2.43 \text{ mm}) \). Thereafter, a mask was applied to strip the AC map from bed and head support as well as noise surrounding the head, followed by rigid co-registration and resampling to the participant's individual Atlas-MRAC map. As the axial FOV differed between the stand-alone PET (155 mm) and PET/MR scanner (250 mm), the \[ ^{68} \text{Ge-MRAC} \] map was completed with the corresponding information concerning the neck and top of the head from the Atlas-MRAC map.

As a common step for all generated MRAC maps, coil and bed AC map templates were then incorporated, applying an in-house MATLAB pipeline (MATLAB R2017a, Mathworks Inc., Natick, MA).

Image reconstruction

The dynamic \( ^{11} \text{C} \)PE2I PET data were reconstructed using time-of-flight OSEM with 2 iterations, 28 subsets, 5 mm Gaussian post-filter, \( 128 \times 128 \) reconstruction matrix and 300 mm FOV. MRAC was performed in four ways as described in the previous section. Further, all appropriate corrections for quantitative image reconstruction were applied.

\[ ^{11} \text{C} \]PE2I image analysis

The methodology and validation for voxel-level analysis of dynamic \( ^{11} \text{C} \)PE2I scans have been previously reported [39, 40].

Following this approach, the reconstructed \( ^{11} \text{C} \)PE2I PET images were realigned to correct for interframe patient movements using an early (0–3 min) \( ^{11} \text{C} \)PE2I summed image as reference using an in-house MATLAB 2018 script. Interframe motion was estimated in this way for the PET images corrected for AC
using $^{68}$Ge-AC and the same transformation were applied to the other three dynamic data sets. Subsequently, the same summed image was used for co-registration of the 3D T1w MRI scan based on a 6-parameter rigid transformation, to achieve positional alignment. Then MR images were segmented into grey matter, white matter, and cerebrospinal fluid using Statistical Parametric Mapping (SPM12; Wellcome Trust Center for Neuroimaging, University College London, UK). Grey matter volumes of interest (VOI) were established on the T1w structural MR images using an automated probabilistic template as implemented in the PVElab software [43] for cortical and limbic regions. For striatal regions, MAPER [44], a technique optimized for segmentation of atrophic brains, was used to achieve a more accurate delineation. All VOIs were projected over the dynamic scans to generate time-activity curves (TACs).

Parametric images were generated from the [$^{11}$C]PE2I scan using receptor parametric mapping (RPM) with cerebellar grey matter as a reference region [45]. RPM is an implementation of the simplified reference tissue model (SRTM; [46]) with a set of predefined basis functions to linearize the model and estimate voxel-wise $R_1$ and $BP_{ND}$ that can be applied to $[^{11}$C]PE2I. The parametric $[^{11}$C]PE2I $BP_{ND}$ images demonstrate specific binding of $[^{11}$C]PE2I to DAT directly proportional to DAT density (availability) and therefore mainly show the deep grey matter of the striatum. The parametric $[^{11}$C]PE2I $R_1$ images display relative cerebral blood flow, which reveals overall brain functional activity. This procedure was repeated for all four $[^{11}$C]PE2I PET data sets. Finally, the grey matter VOIs on the co-registered MR-images were projected on the various parametric $[^{11}$C]PE2I $R_1$ and $BP_{ND}$ images from all four datasets.

**Volumes of interest**

Quantification of $BP_{ND}$ was evaluated separately for the caudate nucleus and putamen as well as for the whole dorsal striatum (volume-weighted average of putamen and caudate). These regions normally have high DAT availability, but a pronounced reduction is often observed in persons with parkinsonism [40].

Evaluation of the quantification of $R_1$ was based on four clusters of VOIs across the brain: anterior cortical regions (cingulate, frontal gyrus), posterior cortical regions (occipital cortex, parietal cortex, and somatosensory-motor cortex), dorsal striatal regions (caudate nucleus, putamen) and limbic regions (amygdala, hippocampus, hypothalamus, and thalamus) [40]. In addition, whole-brain grey matter (WB) was determined as an overall measure.

**Evaluation of MRAC maps**

All participants' MRAC maps were converted to MNI space using SPM12. Mean MRAC images for all four methods were calculated and bias compared to $^{68}$Ge-MRAC was calculated at the voxel level as follows:

\[
Bias(i) = MRAC(i) - MRAC_{^{68}Ge} \quad \text{Eq.1}
\]

where $i$ refers to the three MRAC methods being compared to $^{68}$Ge-MRAC.
Attenuation maps were assessed on soft tissue and bone compartments. A large VOI was drawn over the GE-AC map soft tissue and copied to the other AC methods. A bone mask was created by simple segmentation of the ZTE map and slightly eroded (2 iterations) to reduce the probability of coinciding with other tissues. The bone mask was then transferred to all other AC methods. Mean bias values were calculated for both soft tissue and bone.

**Evaluation of $[^{11}\text{C}]$PE2I BP$_{ND}$ and R$_1$ estimates**

$[^{11}\text{C}]$PE2I BP$_{ND}$ and R$_1$ images for each subject were converted to MNI space using SPM12. Mean $[^{11}\text{C}]$PE2I BP$_{ND}$ and R$_1$ images for all four methods were calculated and bias (Eq. 1) compared to $^{68}\text{Ge}$ was calculated at the voxel level for the defined VOIs.

For quantitative assessment, we used relative differences (% bias; see Eq. 2) in BP$_{ND}$ and R$_1$ as a measure of accuracy, while standard deviation of the bias was taken as a measure of precision.

\[
\text{Bias}(\%) = \frac{\text{PET}_{MRAC(i)} - \text{PET}_{^{68}\text{Ge}-MRAC}}{\text{PET}_{^{68}\text{Ge}-MRAC}} \times 100 \quad \text{Eq.2}
\]

with $i$ referring to the three evaluated MRAC methods.

Correlation analysis (Spearman) and Deming regression were used to assess the degree of agreement between BP$_{ND}$ and R$_1$ values obtained using each of the evaluated MRAC methods and the reference method ($^{68}\text{Ge}$-MRAC).

Statistical analysis was performed using GraphPad Prism 6 (GraphPad Software, La Jolla, California). Significant differences in bias ($p < 0.05$) between each evaluated MRAC method and $^{68}\text{Ge}$-MRAC as reference method were assessed using a Friedman test with post-hoc tests (comparison to $^{68}\text{Ge}$-MRAC) and Dunn's correction.

**Evaluation of time-activity curves**

Previous reports indicate that effects of attenuation correction on uptake over time can be inhomogeneous [33, 34, 47, 48] and may potentially affect the accuracy and precision of the parameters estimated by kinetic modelling. We therefore examined relative bias and its SD in $[^{11}\text{C}]$PE2I standardized uptake values (SUV) over time. This was done for striatal regions with a high DAT density and the reference region (cerebellum) used after implementation of Atlas-, ZTE- and MaxProb-MRAC.

**Results**

**MRAC maps**

The MRAC maps for $^{68}\text{Ge}$, Atlas, ZTE and MaxProb of a representative subject are presented in Fig. 1. Each MRAC-map exhibited distinct qualitative features mainly inherent to how the maps were generated.
The $^{68}$Ge-MRAC map displayed images with heterogeneous signal in the soft tissue, typical for transmission AC images obtained on a stand-alone scanner. The ZTE-MRAC map based on MRI methodology had the highest resolution, although the sinus regions are not well defined. The Atlas- and MaxProb MRAC maps were qualitatively similar. Furthermore, $^{68}$Ge and MaxProb MRAC maps were completed with Atlas-based information.

Figure 2 shows the mean bias across all participants in brain attenuation maps for the evaluated MRAC methods. In brain soft-tissue, the smallest mean bias was found for ZTE-MRAC ($2.9 \times 10^{-4}$ cm$^{-1}$) and MaxProb-MRAC ($3.0 \times 10^{-4}$ cm$^{-1}$) closely followed by Atlas-MRAC ($3.3 \times 10^{-4}$ cm$^{-1}$). In bone, Atlas-MRAC yielded the lowest mean bias ($5.6 \times 10^{-4}$ cm$^{-1}$) compared with an approximately two times higher bias for MaxProb-MRAC ($13 \times 10^{-4}$ cm$^{-1}$) and three times higher bias for ZTE-MRAC ($18 \times 10^{-4}$ cm$^{-1}$). In the sinus region, an evident bias was detected in all maps where the highest overestimation was noticed for ZTE-MRAC.

**Binding potential**

Mean parametric $\text{BP}_{\text{ND}}$ images were similar for all MRAC methods (Fig. 3A). Mean bias images of $\text{BP}_{\text{ND}}$ displayed an obvious negative bias in striatum in case of Atlas-MRAC while these images pointed to a relatively small striatal bias for ZTE- and MaxProb-MRAC (Fig. 3B). Various bias patterns between MRAC-methods were found for extrastriatal regions but this might also be due to low DAT density (see Fig. 3B).

The relative bias of the striatal $\text{BP}_{\text{ND}}$ estimates is presented in Figure 4A. Atlas-MRAC resulted in a substantial negative relative bias for caudate and entire striatum, but only a small bias for putamen. For ZTE, a minor relative bias in $\text{BP}_{\text{ND}}$ with a low variability was observed for putamen and striatum, whereas a greater variability between participants was noted for caudate. For all regions, MaxProb showed considerable variability with both positive and negative bias percentages. There was no obvious relationship between the magnitude of the reference values ($^{68}$Ge $\text{BP}_{\text{ND}}$) and bias percentages.

The Deming regression lines demonstrated a high degree of agreement for ZTE- and MaxProb-MRAC compared to the reference method in all brain regions (Fig. 4B). In contrast, the regression lines for Atlas-MRAC exhibited a deviation from the identity line, indicating a negative bias compared to the reference method.

Table 1 lists quantitative values related to accuracy (% bias) and precision (SD of % bias) for estimated $\text{BP}_{\text{ND}}$ values as well as measures of consistency between evaluated and reference MRAC (correlations, regression parameters). ZTE-MRAC results showed little bias for all regions (<2%) with a generally high precision. The highest bias was found for Atlas-MRAC in caudate (approximately −12%) which differed significantly from $^{68}$Ge-MRAC ($p < 0.05$). MaxProb also showed a relatively large mean bias in putamen (about 9%) but did not deviate significantly from $^{68}$Ge-MRAC. MaxProb-MRAC showed the lowest precision in all regions. Only the bias obtained for caudate with the Atlas approach was statistically significant.
In general, strong correlations with $^{68}$Ge-MRAC were established for all three evaluated MRAC- methods in all regions ($r \geq 0.95$).

| Brain region | MRAC   | % bias | SD   | $r$  | Slope | Intercept |
|--------------|--------|--------|------|------|-------|-----------|
| CN           | Atlas  | -12.09*| 5.36 | 0.98 | 0.88  | -0.01     |
|              | ZTE    | -0.85  | 7.41 | 0.95 | 1.07  | -0.18     |
|              | MaxProb| 2.11   | 13.24| 0.98 | 0.98  | 0.06      |
| PUT          | Atlas  | 0.52   | 6.04 | 1.00 | 0.97  | 0.07      |
|              | ZTE    | 1.83   | 3.81 | 0.95 | 1.02  | -0.02     |
|              | MaxProb| 9.19   | 10.78| 1.00 | 0.98  | 0.29      |
| STR          | Atlas  | -5.43  | 3.31 | 0.98 | 0.94  | 0.00      |
|              | ZTE    | 0.30   | 3.95 | 0.97 | 1.05  | -0.11     |
|              | MaxProb| 5.48   | 10.62| 1.00 | 0.99  | 0.17      |

$CN$ caudate nucleus, $PUT$ putamen, $STR$ striatum.

* $p$-value < 0.05.

Estimated $BP_{ND}$-values and relative bias for the evaluated MRAC-methods are illustrated with boxplots in Fig. 5. The median $BP_{ND}$ of the investigated brain regions differed only modestly within regions (Fig. 5A). The relative bias was low for ZTE-MRAC while MaxProb-MRAC showed the lowest precision indicated by the size of the boxes and bars (Fig. 5B).

**Relative delivery**

Mean parametric $R_1$ images, representing relative cerebral blood flow and overall brain activity, are presented in Fig. 6A and show similar patterns for all four MRAC methods. Mean bias images of $R_1$ indicated mostly a positive bias throughout the brain regardless of the MRAC method used (Fig. 6B). Further, these images pointed to a distinct positive bias in the anterior part of the brain for Atlas-MRAC and especially MaxProb-MRAC. Negative bias was evident in the posterior part of the brain for Atlas-MRAC and to a lesser degree for ZTE.
The relative bias of $R_1$ estimates for various clusters of brain regions is displayed in Fig. 7A. Generally, the relative bias of $R_1$ was within a range of $\pm 5\%$. However, for all brain clusters the variability was greater for MaxProb-MRAC compared to the other MRAC methods. $R_1$ estimates of WB had a small bias and variability for all MRAC-methods. The individual regional $R_1$ bias values were generally in the range of $-5$ to $15\%$. Striatal $R_1$ estimates contained mainly a positive bias, while the other regions contained both positive and negative $\%$ bias.

Strong and similar relationships were found between the $R_1$ estimates from the investigated MRAC methods and the reference method (Fig. 7B). All Deming regression lines were close to the line of identity, displaying a high degree of agreement.

Table 2

$R_1$ – Mean $\%$ bias, precision (SD of $\%$ bias) and correlation coefficient ($r$) for all clusters of brain regions when comparing Atlas-, ZTE- and MaxProb-MRAC against $^{68}$Ge-MRAC. Additionally, slope and intercept of Deming regression lines are given.

| Brain region | MRAC | % bias | SD   | $r$  | Slope  | Intercept |
|--------------|------|--------|------|------|--------|-----------|
| WB           | Atlas| 0.44   | 1.67 | 0.98 | 1.12   | -0.10     |
|              | ZTE  | 0.99   | 1.21 | 1.00 | 0.94   | 0.06      |
|              | MaxProb | 1.37    | 2.69 | 0.93 | 1.11   | -0.08     |
| ACR          | Atlas| 1.54*  | 2.85 | 0.98 | 1.10   | -0.07     |
|              | ZTE  | 1.14   | 2.49 | 0.97 | 1.06   | -0.04     |
|              | MaxProb | 2.85*    | 4.12 | 0.96 | 1.07   | -0.03     |
| PCR          | Atlas| -0.95  | 2.91 | 0.97 | 1.05   | -0.05     |
|              | ZTE  | -0.51  | 1.47 | 0.99 | 0.99   | 0.00      |
|              | MaxProb | 1.14    | 4.38 | 0.92 | 1.06   | -0.04     |
| STR          | Atlas| 2.44*  | 2.53 | 0.99 | 0.99   | 0.03      |
|              | ZTE  | 2.71*  | 2.06 | 0.99 | 0.99   | 0.03      |
|              | MaxProb | 3.17*    | 3.67 | 0.98 | 1.01   | 0.02      |
| LR           | Atlas| 2.29*  | 3.26 | 0.97 | 1.03   | -0.01     |
|              | ZTE  | 3.09*  | 3.33 | 0.97 | 1.00   | 0.02      |
|              | MaxProb | 0.35    | 3.94 | 0.98 | 1.06   | -0.04     |

ACR anterior cortical regions, PCR posterior cortical regions, STR striatal regions, LR limbic regions, WB whole brain. * $p$-value $< 0.05$. 

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The outcome of the evaluation of $R_1$ estimates (accuracy, precision and degree of agreement) are given for various clusters of brain regions in Table 2. For all investigated MRAC methods, the mean bias percentages were low and within a range of -1.0 to +3.5%. A modest negative mean bias was found for posterior cortical regions using Atlas- or ZTE-MRAC, whereas all other mean bias values were positive. Based on the SD of the mean bias percentages, ZTE-MRAC showed the highest precision and MaxProb-MRAC the lowest precision, which was consistent for most clusters of brain regions. High correlations between the evaluated MRAC methods and the reference method were attained for all brain regions (0.92-1.00).

Boxplots for estimated $R_1$ values and relative bias are given for all MRAC-methods used in Fig. 8. Only minor differences in median and the variability of $R_1$ estimates were found between the four MRAC-methods within each brain cluster (Fig. 8A). Significant differences in relative bias were noted in striatum for all three MRAC methods relative to $^{68}$Ge-MRAC; in anterior cortical regions for Atlas- and MaxProb-MRAC and in limbic regions for Atlas and ZTE, Table 2 and Fig. 8B.

### Evaluation of time-activity curves

Figure 9 shows the bias and its SD over time in SUV for the three evaluated MRAC methods compared to $^{68}$Ge-MRAC, in striatum and cerebellum. In striatal regions, the biases on TACs had variable shapes: a strong but constant bias over time at around 10% for ZTE, variable average bias over time for Atlas, ranging from +10 to -7% in caudate, and for MaxProb, ranging from +5 to -5% in caudate. Intersubject variability was smallest for ZTE-MRAC and largest for MaxProb-MRAC. Further, in cerebellum both Atlas- and ZTE-MRAC showed a bias with low variation over time and with small intersubject variability, while the opposite was true for MaxProb-MRAC. However, MaxProb-MRAC showed the lowest absolute bias in cerebellum.

### Discussion

**Significance**

The novel opportunities afforded by simultaneous acquisition of PET and MR imaging data on modern hybrid scanners come at the cost of increased difficulty in reconstructing quantitatively correct PET images and parametric maps. This study contributes to solving this problem by quantitatively comparing recently proposed MRAC methods. The results will help users of PET-MR hybrid systems to choose the correction method that is most appropriate for their practice requirements. Specifically, we reconstructed individual parametric [$^{11}$C]PE2I BP$_{ND}$ and $R_1$ images generated by a voxel-wise kinetic modelling approach applied on a dynamic [$^{11}$C]PE2I PET scan using four methods. The main differences with most other reported MRAC evaluation studies are three-fold: (1) acquisition of dynamic data instead of static data; (2) use of individual $^{68}$Ge-transmission AC maps with a direct measurement of 511 keV AC as
reference method in contrast to CT-AC; (3) parametric images providing functional information, related to DAT availability and overall brain activity, whereas standard uptake values (SUV) or ratios to a reference region (SUVr) reflect mostly tracer uptake. The study is pertinent for quantitative dynamic PET/MR imaging in research, but also for our clinical practice because dynamic $^{[1]}$C$^{11}$PET scanning, followed by a kinetic modelling approach, is implemented in the routine clinical evaluation for differential diagnosis of parkinsonian disorders at Uppsala University Hospital.

**Main results**

The evaluation of attenuation maps showed that ZTE- and MaxProb-MRAC agreed best with $^{68}$Ge-AC in brain soft tissue. In bone, Atlas-MRAC showed the lowest and ZTE-MRAC the highest bias. While absolute differences were small in soft tissue (less than 10%), they were larger in bone (up to 16%), with Atlas-AC showing the lowest and ZTE-MRAC the highest bias. The bias in bone may in part be due to the spatial resolution of the different AC images, with skull being more smoothed in the Atlas- and $^{68}$Ge-AC images than in Maxprob- and ZTE-AC images. Since the bone VOI was based on ZTE, it inherently showed lower AC values in Atlas and $^{68}$Ge-AC maps.

For BP$_{ND}$ in striatal regions, mean bias across AC methods ranged from about $-12$ to $+9\%$. For R$_1$, the mean bias ranged from about $+1$ to $+3\%$ in various clusters of regions across the brain for all methods. Values within limits of $-/+/5\%$ are generally regarded as acceptable. Importantly, differences in accuracy and precision between MRAC data sets can in part be explained by differences in shapes of the time activity curves and its SDs.

ZTE-MRAC showed low BP$_{ND}$ bias for all striatal regions (-0.9 to 1.8%). The vendor-provided Atlas-MRAC method appeared to perform well for estimation of BP$_{ND}$-values in putamen, but a severe and significant underestimation was found in BP$_{ND}$ values in caudate (12.1%). In contrast, for MaxProb-MRAC the mean bias was also relatively low in caudate (2.1%) while a substantial, but non-significant, bias was observed in putamen (9.2%). However, MaxProb-MRAC showed higher variability in bias for all regions (see Fig. 4A), and in both estimates of BP$_{ND}$ and R$_1$, indicating a lower precision than ZTE- and Atlas-MRAC. Methods with both a high accuracy and precision are most desirable as this will lead to more robust and reproducible outcome parameters. As such, the higher accuracy of MaxProb in terms of attenuation maps did not translate to higher accuracy for BP$_{ND}$ estimates.

Previously, we evaluated Atlas- and ZTE-MRAC compared to $^{68}$Ge MRAC using static brain $^{[1]}$C$^{11}$PET images from the same group of participants with suspected parkinsonian disorders [32], but using only regional SUV and SUVR (SUV ratios to cerebellar grey matter) as semi-quantitative outcome parameters. In this prior work, ZTE-MRAC was also found to be more reliable than Atlas-MRAC in terms of accuracy, precision, and degree of agreement compared to $^{68}$Ge MRAC. The same clusters of brain regions across the brain were used for R$_1$ in the current study, allowing some comparisons. The largest mean regional biases were found when using SUV, i.e. varying between 6 and 10% for both Atlas- and ZTE-MRAC. This
bias decreased considerably when normalizing SUV to cerebellum, resulting in regional bias percentages of 2.9 to 4.8% for Atlas-MRAC and −1.3–2.6% for ZTE-MRAC.

Only a few prior brain PET/MRI studies have investigated the effects of MRAC methods on accuracy and precision in the context of kinetic modelling of dynamic PET [33, 35–37, 49]. Schramm et al. [49] evaluated ZTE-MRAC and Atlas-MRAC compared to CT-based AC in eight healthy volunteers using a Signa PET/MRI scanner and [18F]PE2I. BPND in striatal regions was estimated using SRTM with cerebellum as reference region. In striatum, the mean bias was 1.5% for ZTE-MRAC and 3.8% for Atlas-MRAC. These results are in line with our study for ZTE-MRAC, but not for Atlas-MRAC where we found a bias of -5.4%. Our Atlas-MRAC results revealed that especially in caudate, the BPND values were severely underestimated for all participants (Fig. 4–5, Table 1), leading to a range of individual biases from −11.0 to -1.0% compared to -1.0 to +9.4 reported by Schramm et al. [49]. The discrepancy in results might be due to differences in the type of participants (patients vs healthy subjects) and methodological aspects such as tracer properties ([11C]PE2I vs [18F]FE-PE2I), definition of brain regions (using Hammers maximum probability atlas in PMOD [50, 51]), and most importantly the reference standard used (68Ge vs CT). However, both studies point out distinctly that ZTE-MRAC performed better than Atlas-MRAC.

Merida et al. [33] assessed the value of a multi-atlas approach (MaxProb-MRAC) compared to a single atlas with CT-based AC as reference method. The study used dynamic PET data from seven healthy participants acquired on a PET/CT scanner without TOF and using the serotonin 5-HT1A receptor tracer [18F]MPPF. SRTM was used for estimation of BPND across the brain, with cerebellar grey matter defined with the Hammers maximum probability atlas [50, 51] and excluding cerebellar vermis which may contain 5-HT1A receptors. Overall, bias of BPND ranged from −2.5–5.0% for MaxProb-MRAC and from −9.3–3.3% for their single-atlas MRAC. For MaxProb, the range of the bias was in good agreement with our results, as was the substantial increase in bias when using a single-atlas MRAC. Furthermore, their single-atlas MRAC caused a severe underestimation of BPND values, as seen for Atlas-MRAC in our study. However, these comparisons between studies need to be interpreted with care because of differences in data acquisition, tracer kinetics and specified VOIs. It should also be noted that this study's single-atlas MRAC implementation is different from Atlas-MRAC in the present work.

Previous reports indicate that the effect of different AC methods over time after injection may be dependent on the varying distribution of the tracer [33, 34, 47, 48]. In addition, any misalignment-induced errors in attenuation correction are not corrected by post-reconstruction frame-by-frame realignment. Although identical motion correction was used for all four AC methods, misalignment-induced errors can vary for different AC methods. These could be two reasons for the differences in accuracy and precision of outcome parameters of kinetic analysis based on the different AC methods. Hence, relative bias and its SD in SUV values over time for striatal regions and cerebellum after implementation of Atlas-, ZTE- and MaxProb-MRAC were assessed. Both relative bias and SD varied over time in different ways for the different regions and methods, especially in caudate and consequently striatum (Fig. 9). MaxProb showed distinct changes over time for the later frames. These findings are in line with the hypothesis that
various MRAC methods are affected differently by the radioactivity distribution in the brain at different time points [33]. In the present study, the biases on TACs have different temporal shapes between regions for Atlas-MRAC and MaxProb, which partially explain their bias in R1 and BPND. For example, for MaxProb, the bias curves for cerebellum and striatum have similar shapes, and bias in the resulting BPND is low (2.1%) whereas bias curves in cerebellum and putamen have different shapes, resulting in a larger bias in BPND for putamen (9.2%) despite the bias for putamen in the TACs themselves being much lower than that of the other two methods. For ZTE, TACs show large, but constant biases over time (around 10% for striatum and 5% for cerebellum). These quantification errors are then compensated when using cerebellum as reference region in kinetic modelling, or SUV ratios over cerebellum. It is noteworthy that the constant-but-high biases on ZTE TACs could have a higher impact when kinetic modelling is performed with arterial input functions or with a reference region other than the cerebellum, where the error compensation between two regions may not take place. In that case, Maxprob-AC may be the optimal method because of its lower absolute bias.

Based on our results it should be noted that the choice of MRAC method may depend on amongst other the aim of the PET examinations, type of participants, tracer and quantification method. The aim of the study determines the requested accuracy and precision of the quantification method required for interpretation of the results. When considering absolute values, MaxProb’s low absolute TAC bias may be particularly important. For ratio or reference region-based methods ZTE’s higher but temporally consistent TAC bias will be an advantage. In case of participants with an abnormal anatomy, e.g. post-trauma or -operative patients, acquisition-based methods like ZTE-MRAC will be preferable. In contrast to stand-alone PET and PET/CT systems it may be difficult to develop a standard MRAC routine for AC in integrated PET/MR systems suitable for all circumstances and tracers. Instead the choice of MRAC method for a specific investigation need to be based on balancing the pros and cons of each approach.

**Methodological Considerations**

There are five major methodological considerations which need to be addressed as they might affect comparisons between MRAC methods and other studies. *First*, we used 68Ge-transmission AC maps with a direct voxel-wise measurement of AC in contrast to CT-AC. A 68Ge transmission scan measures attenuation directly at 511 keV, whereas CT-AC requires a conversion from Hounsfield units to 511 keV attenuation coefficients. Hence, the 68Ge-AC attenuation maps used in the present work can be regarded as the true reference standard for AC. A comparison of 68Ge-AC and CT-AC showed higher radioactivity concentrations when using CT-AC, although of small magnitude, the differences were consistent and significant [8]. This bias should be noted when considering quantitative analysis and comparisons across different imaging modalities. Today CT-AC is more widely accepted in clinical practice, but this might be due to a higher signal to noise ratio and shorter acquisition times compared with 68Ge AC. *Second*, the AC of 0.097 cm⁻¹ measured for soft tissue for 68Ge-MRAC is modestly lower than that for the other investigated MRAC methods, i.e. 0.100 cm⁻¹. The soft tissue value of 0.100 cm⁻¹ was the same as used
in clinical practice for CT-AC. In the previous study with static \([^{11}\text{C}]\text{PE2I}\) PET data [32] the effect of different AC values was investigated. The accuracy of SUV for various brain regions appeared to be considerably higher for both Atlas- and ZTE-MRAC when scaling all AC maps to 0.097 cm\(^{-1}\), but the precision was scarcely affected. When SUV was normalized to cerebellum (SUVR), the accuracy and precision were similar before and after scaling. Even though in the present study outcome parameters are normalized to cerebellum, we cannot exclude the possibility that differences in AC values might have affected the magnitude of the measures of accuracy. Third, AC of sinus regions is vulnerable to misclassification of tissue types and inaccurate registrations of templates/atlas as they are composed of bone, soft tissue, and air [3, 28]. When this mixture of structures is classified as bone, the resulting positive bias can affect cerebellum if the sinus region in question is close [3]. In our study, parametric R\(_1\) and BP\(_{\text{ND}}\) images were generated from the dynamic \([^{11}\text{C}]\text{PE2I}\) scan using a kinetic modelling approach with cerebellum as reference region. In theory, biased AC in sinus regions could therefore have affected the accuracy of the estimated R\(_1\) and BP\(_{\text{ND}}\) values in various regions. However, we believe this effect is modest. For R\(_1\), which displays CBF at an early stage, only a minor bias was noted for all MRAC methods. On the other hand, BP\(_{\text{ND}}\) is related to the specific binding of \([^{11}\text{C}]\text{PE2I}\) to DAT, while the cerebellum is devoid of DAT. Accurate registration of templates/atlas might be hampered by the difficulty of matching skull boundaries in sinus regions. Furthermore, the interindividual variability is large for sinus regions. Inaccurate registrations might confound parameter estimations, particularly in subcortical regions. Fourth, similar to \(^{68}\text{Ge}\)-transmission AC maps, ZTE-MRAC is based on an individual scan in contrast to single- and multiple atlas MRAC approaches. One advantage of a specific AC map for every individual is that it does not depend on a priori anatomical information and assumptions [10, 49]. Multiple atlases should be more reliable than a single atlas, as shown earlier by Merida et al. [33] and also found in our comparison of Atlas- and MaxProb-MRAC. However, methods based on an individual scan are likely to be suitable even for patients with an abnormal brain anatomy (e.g. brain cyst or hydrocephalus) or after surgery (e.g. patients with epilepsy surgery or traumatic brain injury). Fifth, the vendor-provided ZTE- and Atlas-MRAC are under continuous development and reflected the state of the art at the time when the study was conducted. At the time of this writing, the version of ZTE-MRAC as used in the present work (MP26) is commercially available [52], but further developments have already been proposed [53, 54]. Some may have already been implemented but were outside the scope of this study.

Limitations

Our study has some limitations related to design and methods. As for the previous study, we had to deal with differences in axial FOV between scanners related to AC maps for \(^{68}\text{Ge}\)-MRAC (155 mm), MaxProb-MRAC (216 mm) and Atlas- and ZTE-MRAC (250 mm). For this reason, the missing information of the AC maps for \(^{68}\text{Ge}\) (top and neck regions) and MaxProb (neck regions) were completed with corresponding information from the Atlas AC map. Consequently, the lines of response associated with the added parts might have introduced a bias towards Atlas-MRAC, but more in regions outside than inside the brain.
Another limitation is related to head movements during the entire dynamic PET acquisition. The MRI sequences for AC are acquired during the first five minutes of the PET scan to avoid misalignment between MRAC and MRI data. Since frame by frame motion correction was done using identical transformation parameters for all four dynamic datasets any remaining movement induced errors should be the same for all four AC methods. However, any motion-induced errors in attenuation correction are not corrected for using post-reconstruction motion corrected methods. The effects of these may differ for the different AC methods, and this may have affected our results. Further we had only data from a cohort of patients with parkinsonism, some of whom had severe atrophy. In this case MaxProb-MRAC may mislabel cerebral spinal fluid as bone, which could cause a positive bias in cerebellum as a result of inaccurate bone estimation [18], but this positive bias is not seen in our results. It might have been beneficial to study a healthy cohort in addition to the patient cohort, as effects of MRAC method and disease (alterations in DAT availability and overall brain function) were entangled in the current design. It should also be noted that the tracer used, $[^{11}]$CPE2I, allowed only investigation of the impact of the various MRACs on $BP_{ND}$ values in striatal regions which have a high DAT density. From an evaluation perspective it would be beneficial to investigate a tracer for neuroreceptors or transporters widely distributed across the brain in addition to the dopaminergic system. Despite these limitations, this study provides important information on the accuracy and precision of four MRAC methods in a clinical setting with use of dynamic data.

**Future developments**

For the future development of MRAC methods in dynamic brain PET, it would be important to consider diverse neurological applications in larger patient cohorts with specific tracers. The current study comprised data from only nine patients with parkinsonism, which was enough to attain the aim of the study. However, small study populations do not allow subgrouping based on, e.g., the magnitude of accuracy and precision, subtypes of parkinsonian disorders, or other relevant numerical or categorical measures. Application to more complex cases will show whether the developed MRAC methods are likely to perform well in clinical practice. For example, differential diagnosis of parkinsonian disorders might be extremely challenging at an early stage due to the difficulty of distinguishing typical Parkinson’s disease and the atypical subtypes, and the confounding effect of comorbidity with other neurodegenerative and chronic diseases (e.g. dementia and diabetes). For this, it is essential that quantitative values be accurate and precise. Another promising direction is the further development of an individual mapping of linear attenuation coefficients, as suggested by Visvikis et al. [3]. Like CT-AC, most of the reported MRAC-methods disregarded possible heterogeneity in tissue by using AC maps with fixed values assigned to a limited number of tissue types. More detailed attenuation maps might be developed by optimizing the simultaneous acquired information from MRI and PET combined with templates/atlas and machine learning [55, 56]. Advanced MRAC methods would certainly further promote the clinical use of integrated PET/MRI scanners.

**Conclusions**
This study evaluated bias in estimated attenuation maps as well as accuracy, precision and degree of agreement of $^{[1]}\text{C}$$\text{PE2I BP}_{\text{ND}}$ and $R_1$ estimates for three different MRAC methods using a transmission scan with $^{68}\text{Ge}$ rod sources as reference method. In addition, the time-varying bias in SUV values for striatal regions and cerebellum for the three different AC methods was investigated. Absolute bias in attenuation maps was similar for all evaluated MRAC approaches in soft tissue. In bone, Atlas-MRAC had the highest accuracy and ZTE-MRAC had the lowest accuracy. Estimates of $BP_{\text{ND}}$ were inferior for Atlas-MRAC compared to ZTE-MRAC due to substantial bias of estimated values in caudate. Performance was statistically similar for ZTE- and MaxProb-MRAC, but compared to ZTE-MRAC, MaxProb-MRAC had lower precision in both $BP_{\text{ND}}$ and $R_1$ estimates. In terms of absolute SUV values, bias was smallest for MaxProb-MRAC but variability and variation over time were higher than for ZTE-MRAC. In contrast to stand-alone PET and PET/CT systems it may be difficult to develop a standard MRAC routine for AC in integrated PET/MR systems suitable for all circumstances and tracers. Instead the choice of MRAC method for a specific examination needs to be based on balancing the pros and cons of each approach. Further evaluation of MRAC methods in dynamic brain data is warranted. In particular, studies on larger cohorts for diverse neurological applications and use of multiple tracers will be useful.

Abbreviations

AC: Attenuation correction; $BP_{\text{ND}}$: Binding potential (non-displaceable); CBL: Cerebellum; CT: Computer tomography; DAT: dopamine transporter; FDG: Fluorodeoxyglucose; FOV: Field-of-view; MaxProb: Maximum probability algorithm; MRAC: MR attenuation correction; MRI: Magnetic resonance imaging; NEX: Number of excitations; OSEM: Ordered subset expectation maximisation; PET: Positron emission tomography; $R_1$: Relative delivery; rCBF: Regional cerebral blood flow; RPM: Receptor parametric mapping; SRTM: Simplified reference tissue model; TOF: Time-of-flight; UTE: Ultrashort echo time; VOI: Volume of interest; ZTE: Zero echo time; 3D: Three-dimensional

Declarations

Availability of data and materials

João M. Sousa (joao.sousa@surgsci.uu.se) is the corresponding author for the data used in this manuscript.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.
Consent for publication

Not applicable.

Competing interests

ME is an employee of GE Healthcare. HA and ML receive research support and speaker fees from GE Healthcare.

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Authors’ contributions

Concept, design, ethical application: ML, LA and HA; Recruitment of patients: SP, DN, LA; Acquisition of data: JMS, LA, ML; Data analysis: JMS, ME, ML, IM, NC, RAH; Data interpretation: JMS, IM, ML, LA, AH; Draft of the manuscript: JMS, IM, LA, ML; Review of the manuscript: all authors; Approval of the manuscript: all authors.

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Figures
Figure 1

Typical MRAC maps based on 68Ge-, Atlas-, ZTE- and MaxProb approaches
Figure 2

Mean bias across participants in Atlas-, ZTE- and MaxProb-MRAC maps. Positive bias in red and negative in blue.
Figure 3

A. Mean BPND images using 68Ge- and Atlas-, ZTE- and MaxProb-MRAC showing striatal DAT density. B. Mean bias images of BPND illustrating voxel-wise differences in BPND between each MRAC method and 68Ge-MRAC.
Figure 4

A. Relative differences in BPND (% bias) plots of BPND when comparing Atlas-, ZTE- or MaxProb-MRAC to 68Ge-MRAC (gold standard) for striatal brain regions. B. Relationship between BPND using various MRAC-methods and 68Ge-MRAC as reference, where solid lines represent Deming regressions and dashed line identity.
Figure 5

Boxplots for estimated BPND (A) and % bias (B) in BPND when comparing Atlas-, ZTE- or MaxProb-MRAC to 68Ge-MRAC for caudate (CN), putamen (PUT) and entire striatum (STR). Bars and whiskers represent median and 1st and 3rd quartile. * p-value < 0.05.

Figure 6

A. Mean parametric R1 images using 68Ge- and Atlas-, ZTE- and MaxProb-MRAC. B. Mean bias images of R1 illustrating voxel-wise differences in R1 between each MRAC method and 68Ge-MRAC.
Figure 7

A. Relative differences in R1 (% bias) plots of R1 when comparing Atlas-, ZTE- or MaxProb-MRAC to 68Ge-MRAC as gold standard for different clusters of brain regions. B. Relationship between R1 values derived using various MRAC-methods and 68Ge-MRAC as reference, where solid lines represent Deming regressions and dashed line identity.

Figure 8

Estimated R1 (A) and % bias (B) using Atlas-, ZTE- or MaxProb-MRAC compared to 68Ge-MRAC for different clusters of brain regions. Bars and whiskers are median, 1st and 3rd quartile. ACR anterior cortical regions. PCR posterior cortical regions, STR striatal regions, LR limbic regions, WB whole brain. * p-value < 0.05.
Figure 9

Relative bias and standard deviation over time for two striatal regions with high binding of [11C]PE2I (caudate nucleus and putamen) as well as the whole striatum and the used reference region (cerebellum).