Chapter 2

Comparison of HRRT and HR+ Scanners

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Abstract

Purpose: To directly compare HRRT (high resolution brain) and HR+ (standard whole-body) PET only scanners for quantitative brain studies using three tracers with vastly different tracer distributions. Procedures: Healthy volunteers underwent successive scans on HR+ and HRRT scanners (in random order) using either (R)-[11C]verapamil (n=6), [11C]raclopride (n=7) or [11C]flumazenil (n=7). For all tracers metabolite-corrected plasma input functions were generated. Results: After resolution matching, HRRT derived kinetic parameter values correlated well with those of HR+ for all tracers (intra-class correlation coefficients ≥0.78), having a good absolute interscanner test-retest variability (≤15%). However, systematic differences can be seen for HRRT derived kinetic parameter values (range: -13 to +15%). Conclusion: Quantification of kinetic parameters based on plasma input models leads to comparable results when spatial resolution between HRRT and HR+ data is matched. When using reference tissue models differences remain that are likely caused by differences in attenuation and scatter corrections and/or image reconstruction.
2.1 Introduction

The High-Resolution Research Tomograph (HRRT; CTI/Siemens, Knoxville, TN, USA) is a dedicated human brain positron emission tomography (PET) scanner, combining high spatial resolution with good photon detection sensitivity [1]. Although, initially, the HRRT was primarily used for proof of concept studies and for development of new data acquisition and data correction methodologies, more recently there is a growing interest in its use in clinical studies. These studies have illustrated that it is possible to obtain reproducible estimates of parameters such as metabolic rate of glucose consumption or binding potential (BP<sub>ND</sub>) after injection of [18F]FDG and [11C]raclopride, respectively [2–4]. The number of studies comparing parameter estimates with those obtained using other, more established, scanners, however, has been very limited. Furthermore, quantitative performance of the HRRT may depend on tracer characteristics, necessitating a multi-tracer comparison.

In a previous study by Van Velden et al. [5], the quantitative accuracy of the HRRT was compared to that of a whole-body PET scanner, HR+ (CTI/Siemens, Knoxville, TN, USA) [6], for the tracer [11C]flumazenil. This tracer shows high cortical uptake in healthy volunteers. Over the years, the quantitative accuracy of the HR+ scanner has been studied extensively [6–8], it is a system widely used for brain PET studies and it can therefore be seen as a reference [5]. The spatial resolution of the HR+ is comparable to the current PET/computed tomography (CT) scanners widely used. Van Velden et al. concluded that higher parameter values were obtained with the HRRT than with the HR+ scanner using either plasma input or reference tissue models, indicating improved HRRT quantification primarily due to a reduction in partial-volume effects. However, the outcome of reference tissue model analysis may be affected by low counts in the reference region causing bias in the reconstructed HRRT images [9], or by inaccuracies in the attenuation and scatter corrections [10–12]. In recent years, new HRRT attenuation and scatter correction methods were developed [12, 13]. In addition, the use of a resolution model may reduce low-statistics induced bias [14].

The purpose of the present study was to extend the quantitative validation of the HRRT to tracers with completely different kinetics and distribution, namely [11C]raclopride and (R)-[11C]verapamil. The latter one shows low uptake in the brain, as it is a substrate of the efflux transporter P-glycoprotein (Pgp), whilst [11C]raclopride shows high uptake in the striatum and low levels of cortical uptake, as it is a dopamine D<sub>2</sub> receptor antagonist [15]. In addition, the previously published [11C]flumazenil comparison was reanalyzed using the new state-of-the-art reconstructions for the HRRT in order to investigate the impact of resolution-modelling, and new attenuation and scatter corrections on the quantification of the HRRT.
2.2 Materials and methods

2.2.1 Study Design

For each of the three tracers, healthy subjects were scanned twice on a single day. Using essentially identical protocols, subjects were scanned on a HR+ and on the HRRT, in a random balanced order.

Subjects

Seven healthy controls (age ± standard deviation (SD), 27 ± 3 y) were included in the [$^{11}$C]raclopride study, six (61 ± 4 y) in the (R)-[$^{11}$C]verapamil study and seven (53 ± 16 y) in the [$^{11}$C]flumazenil study. Different subjects were used in the three different studies. All subjects received a screening, which included physical and neurological examinations, obtaining a record of their medical history, screening laboratory tests of blood and urine and a structural brain MRI which was evaluated by a neuroradiologist. Subjects were excluded when they showed clinically significant abnormalities of laboratory tests or MRI scan, had a history of major psychiatric or neurological illness or were known to use drugs or medication that affects Pgp function. All studies were approved by the Medical Ethics Review Committee of the VU University medical center, and all subjects gave written informed consent prior to scanning.

2.2.2 Data acquisition

For each subject a structural T1-weighted MRI scan was acquired within one week of PET scanning using a SONATA 1.5 T MRI scanner (Siemens Medical Solutions, Erlangen, Germany) for co-registration and ROI definition purposes. On the day of the PET scan, catheters were placed in the antecubital vein for tracer injection, and in the radial artery for sampling of arterial blood. Subjects were positioned supine on the scanner bed with their head in the centre of the field-of-view. They were instructed to refrain from moving their head during the entire scan procedure. In addition, a head-immobilization device was used to limit head movement. To ensure that head positions were the same during each scan and to keep head motion to a minimum, several points were marked with ink on each subject’s face and the alignment of each point was checked with projected laser lines every 5-10 min [16]. Prior to each emission scan a transmission scan was acquired, which was used for attenuation and scatter correction of the subsequent emission scan. Next, a 60-min emission scan in 3D acquisition mode started simultaneously with an intravenous injection of the tracer. The tracer was administered at a rate of 0.8 mL·s$^{-1}$, which was followed by a flush of 42 mL saline at a rate of 2.0 mL·s$^{-1}$ using an infusion pump (Med-Rad, Beek, The Netherlands). Table 2.1 shows details of injected dose and specific activity. Values were not significantly
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different between HR+ and HRRT scans ($p>0.2$, using a two-tailed student t-test for all four comparisons). Table 2.1 also shows some scanner specific details on the acquisition of transmission and emission scans. During the emission scan, arterial blood was sampled continuously using an on-line blood sampling device [17]. At set times (5, 10, 15, 20, 30, 40 and 60 min after injection), continuous sampling was interrupted briefly to collect manual 10 mL blood samples.

After a light lunch the protocol was repeated on the other scanner. Approximately half of the subjects were first scanned on the HR+ scanner (four out of seven for $[^{11}\text{C}]$raclopride and $[^{11}\text{C}]$flumazenil, three out of six for $(R)$-$[^{11}\text{C}]$verapamil, the other half first on the HRRT scanner.

Table 2.1 – Details on transmission and emission scans.

<table>
<thead>
<tr>
<th>Tracer</th>
<th>HR+</th>
<th>HRRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific activity (GBq mL$^{-1}$)</td>
<td>$(R)$-$[^{11}\text{C}]$verapamil 41 ± 18</td>
<td>38 ± 19</td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$raclopride 97 ± 131</td>
<td>66 ± 44</td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$flumazenil 57 ± 27</td>
<td>52 ± 23</td>
</tr>
<tr>
<td>Injected dose (MBq)</td>
<td>$(R)$-$[^{11}\text{C}]$verapamil 370 ± 28</td>
<td>350 ± 28</td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$raclopride 372 ± 16</td>
<td>359 ± 31</td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$flumazenil 371 ± 25</td>
<td>358 ± 43</td>
</tr>
<tr>
<td>Patient motion between</td>
<td>$(R)$-$[^{11}\text{C}]$verapamil 1.5 ± 1.2</td>
<td>5.0 ± 1.0</td>
</tr>
<tr>
<td>transmission and</td>
<td>$[^{11}\text{C}]$raclopride 2.5 ± 1.1</td>
<td>3.0 ± 1.0</td>
</tr>
<tr>
<td>emission scan (mm)</td>
<td>$[^{11}\text{C}]$flumazenil 4.0 ± 2.2</td>
<td>3.5 ± 1.3</td>
</tr>
<tr>
<td>Transmission scan</td>
<td>All 10 min 2D coincidence scan using three rotating $^{68}\text{Ge}$ rod sources</td>
<td>6 min singles based scan using a fan collimated $^{137}\text{Cs}$ point source</td>
</tr>
<tr>
<td>Emission scan</td>
<td>$(R)$-$[^{11}\text{C}]$verapamil 60 min total duration, 3D mode, divided into 20 time frames</td>
<td>60 min total duration, listmode acquisition, post processed into 20 frames</td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$raclopride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$[^{11}\text{C}]$flumazenil 60 min total duration, 3D mode, divided into 16 time frames</td>
<td>60 min total duration, listmode acquisition, post processed into 16 frames</td>
</tr>
</tbody>
</table>

2.2.3 Data processing

The acquired PET data were histogrammed into 20 time frames ($1\times 15$, $3\times 5$, $3\times 10$, $2\times 30$, $3\times 60$, $2\times 150$, $2\times 300$ and $4\times 600$ s) for $[^{11}\text{C}]$raclopride and $(R)$-$[^{11}\text{C}]$verapamil, or 16 time frames ($4\times 15$, $4\times 60$, $2\times 150$, $2\times 300$, and $4\times 600$ s) for $[^{11}\text{C}]$flumazenil. All PET data were normalized and corrected for scatter, randoms, attenuation, decay and dead time. HR+ data were rebinned using Fourier rebinning and reconstructed using 2D filtered backprojection. Additional smoothing was applied using a 5 mm full width at half maximum (FWHM) Gaussian filter. Reconstructed images consisted of 63 planes of 256×256 voxels with a size of
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1.29×1.29×2.43 mm³. No segmentation was applied during μ-map reconstruction. Scatter was estimated using a 3D single scatter simulation algorithm using both measured emission and transmission data [6]. HRRT data were reconstructed using 3D iterative resolution-modeled ordinary-Poisson ordered-subsets expectation maximization (OSEM) with 12 iterations and 16 subsets [14], taking into account the point spread function of the scanner [18]. Reconstructed images consisted of 207 planes of 256×256 voxels with a size of 1.22×1.22×1.22 mm³. The μ-map used for attenuation correction was reconstructed using a method that introduces scatter correction in the μ-map reconstruction and total variation filtering to the transmission processing [13]. Scatter was estimated using a 3D single scatter simulation algorithm [12]. The use of the above mentioned features, currently available in the latest release of the HRRT Users Community software (version 1.3), is recommended by the HRRT Users Community.

The effective spatial resolution of the HRRT ranges from 1.4 to 2.4 mm FWHM across the transaxial field-of-view when resolution modelling is applied [19], while that of the HR+ ranges from 4.3 to 7.8 mm in 3D mode [6]. In order to compare HR+ and HRRT scanners for the same spatial resolution, HRRT data were analysed with and without smoothing using a 6.5 mm FWHM Gaussian filter.

Previously, for the HRRT, a reconstruction artefact has been reported when head motion occurs between emission and transmission scan when using imaging tracers with high uptake close to the edge of head (e.g. scalp or nose) such as (R)-[11C]verapamil [20]. This artefact originates from the scatter scaling algorithm. Scatter scaling should be restricted to regions that, based on the attenuation sinogram, only contain background activity. In case of a mismatch between transmission and emission data, e.g. due to patient motion, activity can (artificially) be present in those regions. A mismatch between emission and transmission data will therefore lead to an over-subtraction of scatter. In order to minimize this scatter correction scaling artefact, the reconstructed μ-map was dilated by 1-cm around the head. Note, however, that both the scatter and attenuation correction sinogram were calculated based on the original, non-dilated μ-map. Thus, only scatter scaling was based on the diluted μ-map. In order to assess the magnitude of patient motion between emission and transmission scan, the μ-map and the image of last frame of the emission scan were co-registered using VINCI [21]. The total amount of patient motion (in mm) was calculated by \( \sqrt{\Delta x^2 + \Delta y^2 + \Delta z^2} \), where \( \Delta x \), \( \Delta y \) and \( \Delta z \) represent the translation in the x, y and z direction, respectively.

Processing on-line and manually sampled arterial blood data to obtain a metabolite-corrected input function has been described in detail elsewhere (see [22] for (R)-[11C]verapamil, [23] for [11C]raclopride and [24] for [11C]flumazenil. Metabolite analysis was performed in two labs (one located at each scanner) using the same methodology. No significant differences (\( p > 0.05 \), using a two-tailed student t-test) were obtained for either the polar fraction for (R)-[11C]verapamil or the parent fraction for [11C]raclopride and [11C]flumazenil for the five
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time points per tracer that were available for all scans.

2.2.4 Pharmacokinetic analysis

For each subject, the MRI image was co-registered to the corresponding summed image (15-60 min) of the high spatial resolution HRRT scan and to the corresponding summed image of HR+ scan using VINCI [21]. Subsequently, these co-registered MRI images were segmented into grey matter, white matter and extracellular fluid using statistical parametrical mapping (version 8, Institute of Neurology, London, UK). ROIs were defined automatically using PVElab [25] using the Hammers template [26]. ROIs smaller than 1 mL were excluded. In total 59 grey matter regions, subdivided into their left and right constituents (hippocampus, amygdala, medial and lateral part of anterior temporal lobe, parahippocampal and ambient gyri, superior temporal gyrus, middle and inferior temporal gyri, fusiform gyrus, cerebellum, insula, lateral remainder of occipital lobe, anterior and posterior part of gyrus cinguli, middle frontal gyrus, posterior temporal lobe, inferolateral remainder of parietal lobe, caudate nucleus, putamen, thalamus, precentral gyrus, gyrus rectus, orbitofrontal gyri, inferior and superior frontal gyrus, postcentral gyrus, superior parietal gyrus, lingual gyrus, cuneus) except for three regions (brainstem, corpus callosum and total brain), were used in the analysis.

Both $^{[11]}C$raclopride and $^{[11]}C$flumazenil data were analysed using a plasma input and a reference tissue model, $(R)$-$^{[11]}C$verapamil data were analysed using a plasma input model only. Firstly, volume of distribution ($V_T$) was derived using a single-tissue compartment plasma-input model for $(R)$-$^{[11]}C$verapamil and $^{[11]}C$flumazenil [27, 28], and a two-tissue compartment reversible plasma-input model for $^{[11]}C$raclopride [29]. All plasma-input models used blood volume as additional fit parameter. Secondly, the simplified reference tissue model with cerebellum (sum of left and right cerebellum) or pons (manually delineated) as reference region was used to estimate distribution volume ratios (DVR; calculated as BPND+1) for $^{[11]}C$raclopride and $^{[11]}C$flumazenil, respectively [28, 30, 31].

2.2.5 Comparison of kinetic data

Two different estimates of the same kinetic parameter were compared using linear regression analysis. Both square of the Pearson correlation coefficient ($R^2$) and slopes were derived with the intercept fixed as well as not fixed to zero. In addition, the level of consistency was determined for each kinetic parameter using intraclass correlation coefficients (ICC) with a two-way random single measures model (SPSS, Chicago, IL, USA). An ICC close to 1 indicates perfect consistency. Results of these comparisons are reported as mean ± SD. Given the rather small range of $V_T$ values and DVR observed, absolute interscanner test-retest variability was calculated as well [5]. Please note that this test-retest variability does not refer to two scans done on the same scanner, but to two scans done on the same subject on different scanners.
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2.3 Results

Fig. 2.1 shows typical distribution patterns of $(R)$-$[^{11}\text{C}]$verapamil, $[^{11}\text{C}]$raclopride and $[^{11}\text{C}]$flumazenil in the brain. Note the relatively high $(R)$-$[^{11}\text{C}]$verapamil uptake close to the edge of the head (e.g. scalp) as compared with the generally low uptake in most of the brain. Profiles from the images in Fig. 2.1 are shown in Fig. 2.2. The average amount of patient motion
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between transmission and emission scan is given in Table 2.1. Only for (R)-[\textsuperscript{11}C]verapamil, significantly more head motion was observed during the HRRT scans compared to during the HR+ scans (\(p<0.05\), using a two-tailed student t-test).

![Image](image.png)

**Figure 2.2** – Profiles of the images of Fig. 2.1 in the x-direction for a (R)-[\textsuperscript{11}C]verapamil b [\textsuperscript{11}C]raclopride and c [\textsuperscript{11}C]flumazenil. HRRT data were analysed without (G0) and with smoothing using a 6.5-mm (G6.5) full-width-at-half-maximum Gaussian filter.

### 2.3.1 Effects of smoothing

Fig. 2.3 shows the effect of smoothing on \(V_T\) derived from HRRT images. In general, no systematic effect was observed for \(V_T\) values smaller than 1, whereas \(V_T\) values larger than 1 decreased due to smoothing. For high \(V_T\) values the effect of smoothing becomes more pronounced, as these regions have a higher contrast with background and are therefore more sensitive to partial volume effects. However, for (R)-[\textsuperscript{11}C]verapamil, the effect of smoothing is small (average \(V_T\) was 0.74 ± 0.17 and 0.73 ± 0.16 for non-smoothed and smoothed HRRT images, respectively). For this tracer, most brain regions away from the choroid plexus have a low contrast with surrounding regions or background, and are therefore minimally affected by partial volume effects.
2.3.2 (R)-[11C]verapamil data

Despite the dilation of the \( \mu \)-map, data from one subject who moved excessively between the HRRT emission and transmission scan (6 mm) showed a clearly visible reconstruction artefact that originated from the scatter scaling algorithm and had to be excluded from analysis. Therefore, data from five subjects are included in the analysis. Fig. 2.4 shows the comparison between HR+ and HRRT derived \( V_T \) values. After resolution-matching, a clear correlation can be observed (ICC: 0.78), although a negative bias can be seen for HRRT derived \( V_T \) values (slope with fixed intercept to origin: 0.87). Table 2.2 summaries correlation data for the comparison with HR+ data.

2.3.3 [11C]raclopride data

Due to partial coverage of the cerebellum during the HRRT scan, data from one subject had to be excluded from the analysis. For another subject, HPLC analysis of the blood data failed. Therefore, data from five and six subjects were included for plasma-input and reference tissue analyses, respectively. ROI showing a high SD (>10 min\(^{-1}\)) on obtained parameter values (e.g. \( K_1 \), \( k_2 \), \( k_3 \) and \( k_3/k_4 \)) were excluded from plasma-input analysis. On average, 14, 13 and 3% of the ROI were excluded from the analysis of HR+, unsmoothed and smoothed HRRT data, respectively. The comparison between \( V_T \) and DVR derived from HR+ and HRRT images is given in Fig. 2.5. Higher parameter values are found for HRRT compared to HR+ (slope with fixed intercept: 1.33 and 1.24 for \( V_T \) and DVR, respectively). After resolution-matching clear correlations can be seen (ICC ≥ 0.97), although a slope larger than 1 is observed for both kinetic parameters (slope with fixed intercept: 1.15 and 1.11 for \( V_T \) and DVR, respectively). For the reference tissue (cerebellum), average \( V_T \) values of 0.38 ± 0.08 and 0.37 ± 0.08 were obtained from HR+ and resolution-matched HRRT, respectively. Table 2.3 summarises correlations of HRRT data with corresponding HR+ data.

Figure 2.3 – The effect of smoothing HRRT images with a 6.5-mm Gaussian filter (G6.5) on fitted \( V_T \) values for a (R)-[11C]verapamil, b [11C]raclopride and c [11C]flumazenil. Dotted lines indicate lines of identity (LOI). Each subject is presented by a different symbol. The points represent the data of 59 regions of interest.
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Figure 2.4 – A comparison between HR+ and either a original (G0) or b resolution-matched (G6.5) HRRT-derived $V_T$ values for (R)-[11C]verapamil. Dotted lines indicate lines of identity (LOI). Each subject is presented by a different symbol. The points represent the data of 59 regions of interest.

2.3.4 [11C]flumazenil data

Data from five subjects are included in the analysis. Justification for the exclusion of two subjects from either plasma-input or reference-tissue analysis can be found in a previous publication [5]. Fig. 2.6 shows the comparison between HR+ and HRRT derived $V_T$ values and DVR. The HRRT shows higher parameter values compared to HR+ (slope with fixed intercept: 1.29 and 1.08 for $V_T$ and DVR, respectively). After resolution-matching, a clear correlation can be observed (ICC $\geq 0.90$), although either a positive or negative bias can be seen for HRRT derived $V_T$ values and DVR (slope with fixed intercept: 1.12 and 0.91 for $V_T$ and DVR, respectively). For the brain stem, a region similar to the reference tissue (pons), average $V_T$ values of $1.54 \pm 0.16$ and $1.94 \pm 0.20$ were obtained from HR+ and resolution-matched HRRT, respectively. Table 2.4 summarises correlation data for the comparison with HR+ data.

2.4 Discussion

Recent studies clearly have shown that the HRRT is capable of resolving radioactivity concentrations in small brain regions better than most clinical scanners currently in use [4, 32–35]. Due to the higher intrinsic spatial resolution, HRRT images are less affected by partial volume effects. Therefore, these images intrinsically provide a better reflection of true radioactivity concentration distributions than images obtained with scanners with a lower spatial resolution. However, decreasing partial volume effects based on higher spatial resolution are only useful if quantitative characteristics are maintained. Therefore, in the present study, subjects
underwent successive quantitative PET scans on the same day on two different scanners, the HRRT and the HR+, where the latter was used as the reference. A previous interscanner test-retest study using the tracer $^{[11]}$C]flumazenil [16] reported that higher parameter values were obtained with the HRRT than with the HR+ scanner using either plasma input or reference tissue models. However, as $^{[11]}$C]flumazenil shows high cortical uptake, further validation of the HRRT for tracers with a distribution markedly different from $^{[11]}$C]flumazenil was required [5]. As a Pgp substrate, $(R)$-$^{[11]}$C]verapamil is a tracer with low brain uptake, and quantification of its uptake is expected to be more difficult than for $^{[11]}$C]flumazenil. The correlation of HR+ and HRRT derived $V_T$ values yielded only a moderate ICC of 0.62 and 0.78 before and after smoothing the HRRT images, respectively. This correlation is driven primarily by values obtained for thalamus and hippocampus, which showed substantially higher $V_T$ values than the other regions. Uptake in these regions is sensitive to spill-over from the neighbouring choroid plexus (not a region of clinical interest). Exclusion of these regions led to lower ICC (0.45 ± 0.29 and 0.57 ± 0.26 before and after resolution-matching, respectively) due to the limited range (0.4 - 1.2) of remaining $V_T$ values. As all regions distant from the choroid plexus had comparable $V_T$, the impact of smoothing was small due to limited contrast between various regions in the brain. Absolute interscanner test-retest variability was about 14 ± 6%, twice the value found in a previous HR+ only intrascanner test-retest study (7 ± 2%) [22], but similar to the interscanner test-retest variability of the “cortical” tracer $^{[11]}$C]flumazenil (11 ± 4%) [5]. In summary, a good correlation between $V_T$ values derived from both scanners was obtained for this low uptake tracer, with a negative systematic difference of 13% remaining after resolution matching.

Table 2.2 – Mean (and standard deviation in parentheses, over all subjects) of linear regression results, intraclass correlation coefficients (ICC) and interscanner test-retest variability (TRT) of HRRT- versus HR+-derived $V_T$ values for $(R)$-$^{[11]}$C]verapamil.

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>HRRT data$^1$</th>
<th>Intercept fixed to origin</th>
<th>Unfixed intercept</th>
<th>ICC</th>
<th>TRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>$R^2$</td>
<td>Slope</td>
<td>Intercept</td>
<td>$R^2$</td>
</tr>
<tr>
<td>$V_T$ G0</td>
<td>0.88</td>
<td>0.19</td>
<td>0.40</td>
<td>0.29</td>
<td>0.37</td>
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<td></td>
<td>(0.06)</td>
<td>(0.26)</td>
<td>(0.24)</td>
<td>(0.24)</td>
<td>(0.21)</td>
</tr>
<tr>
<td>$V_T$ G6.5</td>
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<td>0.47</td>
<td>0.50</td>
<td>0.19</td>
<td>0.58</td>
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<td></td>
<td>(0.06)</td>
<td>(0.24)</td>
<td>(0.27)</td>
<td>(0.16)</td>
<td>(0.29)</td>
</tr>
</tbody>
</table>

$^1$HRRT data were analysed with (G6.5) and without (G0) smoothing using a 6.5-mm full-width-at-half-maximum Gaussian filter.

In terms of contrast, $^{[11]}$C]raclopride is an example of the other extreme with high uptake in the striatum and much lower uptake in the rest of the brain. HRRT derived $^{[11]}$C]raclopride $V_T$ values and DVR correlated well with corresponding HR+ values (ICC ≥ 0.97 after resolution-
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The slope of the regression line decreased from 1.33 and 1.24 to 1.15 and 1.11 after smoothing for $V_T$ and DVR, respectively, consistent with more pronounced partial volume effects at a lower spatial resolution. However, a positive systematic difference of more than 11% remains. In addition, the high number of instable fits observed in estimation of $V_T$ may indicate temporally variant biases that are not properly accounted for in the kinetic analyses. Unlike the interscanner test-retest variability of $(R)$-[11C]verapamil, the absolute inter-scanner test-retest variability of about 9 ± 2% in DVR was similar to the value found in a previous HRRT only study that focussed on $B_P_{ND}$ (7 ± 2%) [2], and lower than the inter-scanner test-retest variability of [11C]flumazenil (12 ± 5%) [5].

Figure 2.5 – A comparison between HR+ and either original (G0) (a and c) or resolution-matched (G6.5) (b and d) HRRT-derived (a and b) $V_T$ and DVR values (c and d) for [11C]raclopride. Dotted lines indicate lines of identity (LOI). Each subject is presented by a different symbol. The points represent the data of 59 regions of interest.
Table 2.3 – Mean (and standard deviation in parentheses, over all subjects) of linear regression results, intraclass correlation coefficients (ICC) and interscanner test-retest variability (TRT) of HRRT- versus HR+-derived kinetic parameter values for $[^{11}C]$raclopride.

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>HRRT data$^1$</th>
<th>Intercept fixed to origin</th>
<th>Unfixed intercept</th>
<th>ICC</th>
<th>TRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope $R^2$</td>
<td>Slope Intercept $R^2$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V_T$</td>
<td>G0</td>
<td>1.33 (0.08) 0.94 (0.02)</td>
<td>1.36 (0.68) 0.82 (0.09)</td>
<td>0.88</td>
<td>16 (3)</td>
</tr>
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<td></td>
<td>G6.5</td>
<td>1.15 (0.04) 0.98 (0.01)</td>
<td>1.01 (0.50) 0.82 (0.03)</td>
<td>0.97</td>
<td>12 (3)</td>
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<td>$DVR$</td>
<td>G0</td>
<td>1.24 (0.03) 0.93 (0.02)</td>
<td>1.58 (0.09) 0.54 (0.11)</td>
<td>0.98</td>
<td>13 (2)</td>
</tr>
<tr>
<td></td>
<td>G6.5</td>
<td>1.11 (0.03) 0.98 (0.01)</td>
<td>1.17 (0.05) 0.09 (0.05)</td>
<td>0.98</td>
<td>9 (2)</td>
</tr>
</tbody>
</table>

$^1$HRRT data were analysed with (G6.5) and without (G0) smoothing using a 6.5-mm full-width-at-half-maximum Gaussian filter.

In the previous analysis of the interscanner test-retest study of the tracer $[^{11}C]$flumazenil using different attenuation and scatter corrections and no resolution modelling [16], it was shown that the slope with fixed intercept reduced from 1.29-1.11 to 1.04-1.00 and from 1.04-1.04 to 0.90-0.92 (depending on the HRRT reconstruction algorithm used) for plasma-input and reference tissue models, respectively. The results of the present study were very similar, with a reduction in the slope from 1.29 to 1.12 and from 1.08 to 0.93 for $V_T$ and DVR, respectively. However, $R^2$ for $V_T$ and DVR were slightly poorer in the current comparison ($\geq 0.95$ and $\geq 0.90$ after resolution-matching for the previous and current analysis, respectively). The same trend is observed for the test-retest variability. These results indicate that there is only a small additional benefit of using resolution-modelling and/or the new attenuation and scatter corrections in relation to HR+ quantification for this tracer. The remaining negative systematic difference of 7% in HRRT DVR values point to a likely problem with quantification in the reference region, the pons. The 29% higher brain stem $V_T$ for resolution-matched HRRT images compared with HR+ data appears to be the reason for this large difference in DVR.

The higher systematic differences and higher interscanner test-retest variability might be explained by many possible deficits in either system, but likely arise from the HRRT. The results from phantom studies on the HR+ were shown to be quite favourable [6–8]. For the HRRT, however, a previous phantom study showed that, due to the non-negativity constraint of the reconstruction algorithm, bias up to -14% and +28% might occur at low noise equivalent count rates in gray and white matter regions, respectively [10]. The use
of a resolution model has been shown to reduce low-statistics induced bias in $BP_{ND}$ for a different tracer from -10 to -4% in HRRT human brain studies [14].

Table 2.4 – Mean (and standard deviation in parentheses, over all subjects) of linear regression results, intraclass correlation coefficients (ICC) and interscanner test-retest variability (TRT) of HRRT versus HR+ derived kinetic parameter values for $[11\text{C}]$flumazenil.

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>HRRT data(^1)</th>
<th>Intercept fixed to origin</th>
<th>ICC</th>
<th>TRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>$R^2$</td>
<td>Slope</td>
<td>Intercept</td>
</tr>
<tr>
<td>$V_T$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G0</td>
<td>1.29</td>
<td>0.84</td>
<td>1.02</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.10)</td>
<td>(0.09)</td>
<td>(0.52)</td>
<td>(0.35)</td>
</tr>
<tr>
<td>G6.5</td>
<td>1.12</td>
<td>0.86</td>
<td>0.84</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>(0.10)</td>
<td>(0.07)</td>
<td>(0.43)</td>
<td>(0.36)</td>
</tr>
<tr>
<td>DVR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G0</td>
<td>1.08</td>
<td>0.82</td>
<td>0.85</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>(0.16)</td>
<td>(0.08)</td>
<td>(0.45)</td>
<td>(0.36)</td>
</tr>
<tr>
<td>G6.5</td>
<td>0.93</td>
<td>0.83</td>
<td>0.68</td>
<td>0.49</td>
</tr>
<tr>
<td></td>
<td>(0.15)</td>
<td>(0.06)</td>
<td>(0.37)</td>
<td>(0.31)</td>
</tr>
</tbody>
</table>

\(^1\)HRRT data were analysed with (G6.5) and without (G0) smoothing using a 6.5-mm full-width-at-half-maximum Gaussian filter.

Secondly, previous HRRT attenuation correction strategies misclassified thin bones, e.g. those found in the lower part of the skull, on reconstructed $\mu$-maps [10, 11]. Compared to CT-based attenuation, correction the newly developed HRRT attenuation method reduced the error in quantification from 4 to 1% on average, although errors up to 9% can be observed for some regions of interest [13]. Thirdly, the amount of random and scattered events for the HRRT is higher than those observed for the HR+ [36]. This might be explained by the use of a neuro-shield during HR+ studies that reduces the effects of the outside field of view activity, thereby lowering the amount of scattered and random events. Errors in HRRT quantification because of outside field of view activity can lead up to 30% [37]. Finally, systematic differences could arise from the resolution matching when a spatial invariant Gaussian filter is used, since the spatial resolutions of the two scanners vary across the field-of-view to different extents [1, 6, 19]. In order to estimate the uncertainty on the systematic differences arising from the approximate resolution matching, HRRT data were also smoothed using a 7 mm FWHM Gaussian filter. The difference between systematic differences obtained when HRRT data were smoothed using either a 6.5 or 7 mm Gaussian filter was less than 2% (Table S5). It is therefore unlikely that the use of a spatial variant Gaussian filter will have a large impact on the results from the present study. Nevertheless, the need for more sophisticated reconstruction algorithms, such as AB-OSEM or NEG-ML [38, 39], and/or
Comparison of HRRT and HR+ Scanners Discussion

scatter and attenuation correction algorithms [11, 40] for high-resolution brain PET studies remains.

Figure 2.6 – A comparison between HR+ and either original (G0) (a and c) or resolution-matched (G6.5) (b and d) HRRT-derived (a and b) $V_T$ and DVR values (c and d) for $[^{11}\text{C}]$flumazenil. Dotted lines indicate lines of identity (LOI). Each subject is presented by a different symbol. The points represent the data of 59 regions of interest.

Note that the data in the present study were not corrected for head motion. As demonstrated with $(R)$-$[^{11}\text{C}]$verapamil [20], this not only deteriorates the effective spatial resolution, but can also lead to artefacts (i.e. impaired quantitative accuracy) in the HRRT images due to incorrect scaling of the scatter correction. As shown in this study, dilation of the $\mu$-map can minimize the scatter correction scaling artefact observed for $(R)$-$[^{11}\text{C}]$verapamil studies when head motion is small (<6 mm). Although, for $(R)$-$[^{11}\text{C}]$verapamil, a poorer spatial resolution only had a minimal effect on $V_T$ (Fig. 2.3a), further improvement in the accuracy of tracer kinetic analysis might be expected when motion correction is applied. The findings and recommended improvements to software may be applicable to the more modern clinical
PET scanners, e.g. PET/CT and PET/MRI. As research is aimed at improving the spatial resolution of PET scanners, the acquired data will likely be sparse and, consequently, may suffer from bias when using iterative reconstructions with non-negativity constraints [9, 41]. In addition, since bone tissue cannot easily be accounted for during MRI-based attenuation correction, PET/MRI quantification may be hampered in the vicinity of the skull [42]. Therefore, validating modern PET systems against more quantitatively robust PET systems using clinical studies with various tracer distributions is of utmost importance, particularly for kinetic analyses.

2.5 Conclusion

In this study a validation of the HRRT for quantitative brain studies was performed for three tracers with markedly different brain kinetics and tracer distributions. \((R)\)-\([^{11}\text{C}]\)verapamil showed a 13% negative systematic difference after resolution matching with an absolute interscanner test-retest variability of 14%, while \([^{11}\text{C}]\)raclopride showed an 11 to 15% positive systematic difference after resolution matching with an absolute interscanner test-retest variability of 9 to 12%. Reanalyzing the test-retest \([^{11}\text{C}]\)flumazenil dataset with current state-of-the-art attenuation and scatter correction methods, and reconstruction algorithms did not result in a substantial improvement in the observed systematic difference in reference tissue model based kinetic parameters, indicating a need of further improved attenuation and scatter corrections and/or reconstruction algorithms for high-resolution PET imaging.
2.6 Supplementary material

Table S5 – Mean (and standard deviation in parentheses, over all subjects) of linear regression results, intraclass correlation coefficients (ICC) and interscanner test-retest variability (TRT) of HRRT versus HR+ derived kinetic parameter values for $[^{11}C]$flumazenil.

<table>
<thead>
<tr>
<th>Kinetic parameter</th>
<th>Tracer</th>
<th>intercept fixed to origin</th>
<th>ICC (%)</th>
<th>TRT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Slope</td>
<td>$R^2$</td>
<td>Slope</td>
</tr>
<tr>
<td>$V_T$</td>
<td>(R)-$[^{11}C]$verapamil</td>
<td>0.87</td>
<td>0.47</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.06)</td>
<td>(0.24)</td>
<td>(0.27)</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$raclopride</td>
<td>1.14</td>
<td>0.97</td>
<td>0.97</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.04)</td>
<td>(0.03)</td>
<td>(0.48)</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$flumazenil</td>
<td>1.14</td>
<td>0.86</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.10)</td>
<td>(0.06)</td>
<td>(0.42)</td>
</tr>
<tr>
<td>DVR</td>
<td>$[^{11}C]$raclopride</td>
<td>1.12</td>
<td>0.98</td>
<td>1.16</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.03)</td>
<td>(0.01)</td>
<td>(0.04)</td>
</tr>
<tr>
<td></td>
<td>$[^{11}C]$flumazenil</td>
<td>0.91</td>
<td>0.85</td>
<td>0.68</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0.14)</td>
<td>(0.05)</td>
<td>(0.36)</td>
</tr>
</tbody>
</table>
Bibliography


BIBLIOGRAPHY


