The spatial resolution of PET devices is limited by a number of physical factors (Moses 2011). First, the dimensions of the detector crystals, including the thickness, are finite. Second, the annihilation photons are not perfectly co-linear, that is, they are not emitted exactly 180° apart. Third, the annihilation photon may strike the crystal at a non-orthogonal angle, resulting in an 'effective' crystal size larger than the actual size; this is known as the parallax, or depth-of-interaction, effect. Fourth, the photon may scatter within the detector crystal. Fifth, the emitted positron travels a finite distance (the positron range) prior to annihilation.

The total blurring from the above factors can be measured as a point spread function (PSF), either in image space (Reader et al. 2003) or in projection space (Panin et al. 2006), and can be used as a resolution model within iterative image reconstruction in order to improve the spatial resolution of PET images. For typical clinical PET-CT scanners and the most commonly used radioisotope, fluorine-18, the overall contribution of the positron range is the major contributor to the PSF.
range to the spatial resolution is small. This is because the mean (maximum) positron range for fluorine-18 is 0.57 (2.16) mm in water (Cal-González et al 2013), which is an order of magnitude smaller than the spatial resolution of 4–5 mm full-width-at-half-maximum (FWHM) of such scanners. However, high-resolution scanners, such as the high resolution research tomograph (HRRT, Siemens) and the Biograph Vision (Siemens), have resolutions of approximately 2.5 mm (de Jong et al 2007) and 3.2 mm (Casey et al 2017) FWHM, respectively. Radioisotopes such as oxygen-15, gallium-68 and rubidium-82 have much longer positron ranges of 2.34 (7.92) mm, 2.69 (9.06) mm and 5.33 (16.5) mm in water, respectively. These result in a greater contribution of the positron range to the resolution model, which is radioisotope-specific. In principle, the PSF can be measured for all radioisotopes, but in practice this can be challenging, particularly for very short lived radioisotopes such as for oxygen-15 and rubidium-82 (half-lives of 122.24 and 76.38 s, respectively).

Monte Carlo (MC) simulations have been used to describe the positron range distribution (PRD) (Jodal et al 2012, Cal-González et al 2013). Different authors have used different MC methods and empirical functions to describe the PRDs, and thus reported differences in the positron ranges as reviewed in Cal-González et al (2013).

The PRD can be described as a spherically symmetric three-dimensional (3D) probability distribution of the distance travelled, $r$, from the point of positron emission before annihilation. In Cal-González et al (2013), an analytical expression for the distribution function (representing the number of annihilations at a given radial distance) was used:

$$g_3 (r) = C \cdot \left[ (a \cdot r + 1) \cdot \left[ 1 - \frac{r}{\xi_0} \right]^n - \frac{\xi}{\xi_0} \right]$$

(1)

where the function described by equation (1) and the parameters $C, a, \xi_0, \xi$, and $n$ are empirical and are provided for different radioisotopes ($^{18}\text{F}, ^{11}\text{C}, ^{15}\text{N}, ^{18}\text{O}, ^{68}\text{Ga}$ and $^{82}\text{Rb}$).

In Jodal et al (2012), using a different MC simulation code, 2D PRD distributions were simulated for the 2D distance $\delta$ in a plane from the point of positron emission as:

$$g_{2D} (\delta) = (2 \cdot A \cdot \delta + B) \cdot \exp \left( -A \cdot \delta^2 - B \cdot \delta \right)$$

(2)

where equation (2) and the parameters $A$ and $B$ are empirical and determined for a number of conventional PET radioisotopes ($^{18}\text{F}, ^{11}\text{C}, ^{15}\text{N}, ^{18}\text{O}, ^{68}\text{Ga}, ^{62}\text{Cu}$ and $^{82}\text{Rb}$) and which was later extended to other radioisotopes (e.g. $^{22}\text{Na}, ^{94m}\text{Tc}, ^{64}\text{Cu}$ and $^{86}\text{Y}$) in Jodal et al (2014). More details are presented in section A.1 of the supplementary material (stacks.iop.org/PMB/63/24NT01/mmedia).

We have previously developed a method to measure and model spatially variant PSFs across the entire field of view (FOV) of a PET scanner in image space using an array of printed point sources (Kotasidis et al 2013). In this work, the PSF was modelled as a double 3D Gaussian function with parameters dependent on the radial position within the FOV. The work was initially conducted using two PET/CT scanners, the Siemens Hirez and TrueV Biograph scanners, and subsequently extended to the dedicated brain HRRT scanner (Angelis et al 2013). We followed the previously reported method to measure spatially variant PSFs for both fluorine-18 and carbon-11 (Kotasidis et al 2014) using an inkjet printer with 1–2 ml of ink containing 200 MBq of fluorine-18 or 1000 MBq of carbon-11 within a modified printed cartridge was used to print a rectangular grid of point sources of 1 mm diameter and 18 mm apart on plain paper. The paper with printed point sources was inserted between two 5 mm thick acrylic sheets to act as material for positron annihilation. The method was modified for gallium-68 produced using a generator. First, the eluted radioactive solution was concentrated by a factor of ten to 0.5 GBq ml$^{-1}$ using methods presented in Mueller et al (2012). Second, to account for the longer positron range, the thickness of the acrylic sheets was increased to 10 mm and the point sources were printed 24 mm apart in a hexagonal pattern (figure 1). For fluorine-18 and carbon-11, the 15 (radially) by 9 (axially) rectangular grids of point sources were positioned so that the central row of points were aligned with the central axis of the scanner. This allowed the measurement of the PSFs at eight unique discrete radial positions and nine axial positions. For gallium-68, we were able using alternate rows radially to measure the PSFs at 11 unique discrete radial positions and eight axial positions.
Data acquisition and image reconstruction
Data were acquired in list mode (LM) over 20 min for fluorine-18, 60 min for carbon-11, and 120 min for gallium-68, followed by a 6 min transmission scan using a rotating $^{137}$Cs point source (figure 1). Different scan times were used for each acquisition to account for the different half-lives of the radioisotopes and match the count level per point source of the fluorine-18 dataset. Following listmode data histogramming (default options: axial compression of 9, maximum ring difference of 67), image reconstruction was performed using the HRRT user community software (HRRT_U v1.3) using the ordinary Poisson ordered subsets expectation maximisation algorithm (OP-OSEM) with 10 iterations and 16 subsets (Hong et al 2007). The PET images were reconstructed into a $256 \times 256 \times 207$ matrix containing 1.218 75 mm isotropic voxels. All reconstructions were performed with corrections for scatter and attenuation.

Estimation of radioisotope-specific PSFs from published PRD data
The radioisotope-specific PSFs were calculated using the PRDs reported in Jodal et al (2012) and Cal-González et al (2013) as follows. For Cal-González et al (2013), the 3D PRD was calculated using equation (1):

$$PRD_{3D}(x, y, z) = PRD_{3D}(r) = \frac{\epsilon_{3D}(r)}{4\pi r^2}$$

with $r = \sqrt{x^2 + y^2 + z^2}$. For Jodal et al (2012), the 2D PRD defined by equation (2) was projected to 1D using:

$$PRD_{1D}(x) = \int_{-\infty}^{\infty} \left(2 \cdot A \cdot \delta + B\right) \cdot \exp \left(-A \cdot \delta^2 - B \cdot \delta\right) \cdot dy$$

where $\delta = \sqrt{x^2 + y^2}$. The spherical symmetry of the PRD and a generalisation of the Fourier Slice Theorem were then used to populate the Fourier transform of the 3D PRD using:

$$\text{PRD}_{3D}(\xi_x, \xi_y, \xi_z) = \text{PRD}_{1D}(\xi_r)$$

where $\xi_r = \sqrt{\xi_x^2 + \xi_y^2 + \xi_z^2}$ and $\text{PRD}_{1D}(\xi_r)$ is the 1D Fourier transform of $PRD_{1D}(r)$ and $\text{PRD}_{3D}(\xi_x, \xi_y, \xi_z)$ is the 3D Fourier transform of $PRD_{3D}(x, y, z)$. Specifically, the 3D Fourier transform of the kernel is equal to the 1D Fourier transform of $PRD_{1D}(x)$ along all lines going through the origin. Finally, for both calculated PRDs, the isotope specific PSFs were estimated in Fourier space using:

$$\text{PSF}_{3D, Isotope}(\xi_x, \xi_y, \xi_z) = \frac{\text{PSF}_{3D, F-18}(\xi_x, \xi_y, \xi_z) \cdot \text{PSF}_{3D, Isotope}(\xi_x, \xi_y, \xi_z)}{\text{PRD}_{3D, F-18}(\xi_x, \xi_y, \xi_z)}$$

where $\text{PSF}_{3D, Isotope}$ is the 3D Fourier transform of the radioisotope-specific PSF, $\text{PSF}_{3D, Isotope}(x, y, z)$, which was measured for fluorine-18 (with steps summarised in figure 2 of supplementary material).
Quantification of PSF resolution
For both the measured and estimated PSFs, a sum of two 3D Gaussian functions was fitted to the data using:

\[
\text{PSF}(x) = \sum_{i=1}^{2} \lambda_i \cdot p_i(x, \mu_i, \Sigma_i) \sum_{i=1}^{2} \lambda_i = 1
\]

\[
p_i(x, \mu_i, \Sigma_i) = \frac{1}{(2\pi)^{\frac{3}{2}} |\Sigma_i|^{\frac{1}{2}}} \cdot \exp\left(-\frac{1}{2} \cdot (x - \mu_i)^T \cdot \Sigma_i^{-1} \cdot (x - \mu_i) \right)
\]

\[
\mu_i = \begin{pmatrix} \mu_{i1} \\ \mu_{i2} \\ \mu_{i3} \end{pmatrix} \quad \Sigma_i = \begin{pmatrix} \sigma_{i1}^2 & 0 & 0 \\ 0 & \sigma_{i2}^2 & 0 \\ 0 & 0 & \sigma_{i3}^2 \end{pmatrix}
\]

where \( x \) is a 3D displacement vector and \( \mu_i \) and \( \Sigma_i \) are the mean vectors and covariance matrices, respectively, in radial, tangential, and axial directions for each Gaussian distribution and, is dependent on the position of the PSF in the FOV. The \( \lambda_i \) terms in the equation are positive weights for the two Gaussians functions that add up to 1. \( \Sigma_i \) is assumed to be diagonal due to scanner geometry, with each term on the diagonal of the variance matrix equal to the square of the standard deviation in each direction. The resulting 13 parameters were estimated for each PSF at each spatial location using an algorithm based on the expectation-maximisation (EM). For each parameter, the mean values across the radial sampled positions were fitted to a fourth order polynomial in order to parameterize the system response at every location within the FOV with the assumption of rotational and axial invariant PSFs (Angelis et al. 2012). A PSF map for any point in the FOV could thereby be generated.

Using the fitted PSFs, differences between the measured and estimated PSFs at different radial offsets were quantified using FWHM and full-width-at-tenth-maximum (FWTM) in the tangential, radial and axial directions. All fits and analysis were performed using in-house developed tools in Matlab R2014b (The MathWorks Inc., Natick, Massachusetts). An example of measured PSFs and fitted 3D Gaussian profiles for gallium-68 are presented in figure 2.

Results
The results for the radial, tangential, and axial FWHM (top row) and FWTM (bottom row) are shown in figure 3 for the three radioisotopes at different radially sampled positions. For fluorine-18, the average axial measurements are shown for each measured radial position. For carbon-11 and gallium-68, the measured values are compared with the values estimated from the resolution kernels using the PRDs from both Jodal et al. (2012) and Cal-González et al. (2013).

As expected, we saw an increase in the values of FWHM and FWTM as the positron range increased. For carbon-11, at a radial offset of 1.8 cm from the center of the FOV, the radial, tangential, and axial FWHM of the PSF are 2.82, 2.60, and 2.86 mm, respectively, and the FWTM of 5.31, 5.25, and 5.40 mm, respectively. The radial, tangential, and axial FWHM increase to 3.48, 3.09, and 3.63 mm, respectively, and the FWTM to 6.60, 5.79, and 6.24 mm, respectively, at 9.6 cm.

For both carbon-11 and gallium-68, good agreement was obtained between the measured FWHM and FWTM values and those estimated using the PRDs from Cal-González et al. (2013) for radial offsets less than 10 cm. Specifically, the mean FWHM and FWTM differences ranged from −3% to +6% for carbon-11 and from −6% to +7% for gallium-68, with the largest differences corresponding to the points further away radially from the centre of the FOV.

Larger differences were observed when using the PRDs from Jodal et al. (2012), with differences ranging from −4% to +13% for the FWHM and +10% to +20% for FWTM for gallium-68. For carbon-11, better agreement was obtained with differences ranging between +2% to +7% for FWHM and +1% to +10% for FWTM.

Discussion
We have been able to estimate the spatially variant PSF of different radioisotopes by combining measured data for fluorine-18 with the published data of PRDs calculated using MC simulations, with the approach validated for carbon-11 and gallium-68 by comparing the results with measured data using an HRRT scanner. These radioisotopes specific PSFs can be incorporated into image reconstruction with resolution modelling to improve the spatial resolution of the reconstructed images (Reader et al. 2003, Kotasidis et al. 2011). Alternatively, these
PSFs can be used within partial volume correction algorithms to correct for spill-out and spill-in effects. As the spatial resolution of PET scanners improves and as radioisotopes with longer positron range such as oxygen-15, gallium-68 and rubidium-82 are used, the contribution of positron range to the PSFs becomes more important. Under these conditions, radioisotope-specific PSFs should be used in order to recover fully the spatial resolution. However, for very short lived radioisotopes such as oxygen-15 and rubidium-82, it is very challenging to measure the PSFs experimentally and thus an alternative approach is needed. Having validated our approach for carbon-11 and gallium-68, it would seem reasonable to expect that the approach would also work well for very short lived radioisotopes emitting positrons of a similar energy (e.g. oxygen-15).

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**Figure 2.** Representative example of 1D sections through the voxel with maximum value in the radial, tangential and axial directions for the measured data and the fitted 3D double Gaussian function for two gallium-68 points centred axially in the FOV and located at 1.2 cm (top row) and 9.6 cm (lower row) transaxially from the centre. The FWHM and FWTM calculated values are displayed in each graph. HRRT voxel sizes are isotropic and 1.21875 mm in size.

**Figure 3.** FWHM (top row) and FWTM (bottom row) averaged over the axial location versus radial offset in the radial (i) and (iv), tangential (ii) and (v) and axial (iii) and (vi) directions. Data are plotted for fluorine-18 (red), carbon-11 (green) and gallium-68 (blue) and for the measured data (star), and when estimated using the PRDs from Cal-González et al (2013) (open circle) and Jodal et al (2012) (cross).
We achieved better agreement between the measured and estimated PSFs when using the PRDs of Cal-González et al. (2013) than when using the PRDs of Jodal et al. (2012), with more pronounced differences for gallium-68 and FWTM values. Cal-González et al. (2013) also observed differences when comparing the $g_{3D}(r)$ distribution profiles among published methods for different radioisotopes. Such differences could be due in part to different assumptions and the details of the MC simulations. For instance, in the work of Jodal et al. (2012), the MC simulations included positronium formation which travels further before annihilation and which was not included in the simulations of Cal-González et al. (2013). Another explanation for the differences observed are the different empirical functions used to describe the positron range. In particular, small errors in the functions that describe the tails of the distributions, particularly in 2D, can have large effects on the tails of the estimated PSFs.

A limitation of our work is the use of a 3D double Gaussian function to model the PSFs, which was done to interpolate between sampled locations and to improve the precision of the FWHM and FWTM. The use of two Gaussian distributions with different kernel widths and unconstrained means enables modelling of an asymmetric PSF distribution, as commonly observed with measured PSFs. Previous results with fluorine-18 and carbon-11 showed that a 3D double Gaussian model provides a good description of the PSFs for the HRRT. However, simulated PRDs are observed to be not strictly Gaussian in shape and with the longer positron range of gallium-68 the double Gaussian model may not accurately describe the PSFs. Nevertheless, we used this model for both the estimated and measured PSFs with such errors common to both sets of PSFs and we observed only small differences for the PRDs from Cal-González et al. (2013).

**Conclusion**

By combining the simulated PRDs available in the literature and spatially variant PSF measurements for fluorine-18, we were able to estimate and experimentally validate spatially variant radioisotope-specific PSFs for carbon-11 and gallium-68 using a high-resolution brain PET scanner. This approach can be used to estimate the PSF of radioisotopes emitting a positron with a similar energy but with a half-life too short to be experimentally measured such as for oxygen-15.

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