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# Optimized Sampling for High Resolution Multi-Pinhole Brain SPECT with Stationary Detectors

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## Abstract

Brain perfusion SPECT can be used in the diagnosis of various neurologic or psychiatric disorders, e.g. stroke, epilepsy, dementia and posttraumatic stress disorder. As traditional SPECT provides limited resolution and sensitivity, we recently proposed a high resolution focusing multi-pinhole clinical SPECT scanner dubbed G-SPECT-I (Beekman *et al* 2015). G-SPECT-I achieves data completeness in the scan region of interest by making small translations of the patient bed while using projections from all bed positions together for image reconstruction. A strategy to restrict the number of bed translations is desired to minimize overhead time. Previously we presented optimized bed translation paths for focused partial brain imaging, while here we focus on whole brain imaging which is the common procedure in perfusion studies. Thus, a series of noise-free scans using a reduced number of bed positions were simulated and compared to an oversampled reference scan acquired with 128 bed positions. Noisy simulations were included to validate the utility of the optimized sequences in more realistic situations. Brain Uptake Ratios (BURs) and left-right Asymmetry Indices (AIs) in 51 selected Regions of Interest (ROIs) were calculated for assessment. Results show that images were barely affected by decreasing the number of bed positions from 128 down to 18 (mean deviation from the reference of only 2.2% and 1.5% for the BUR and AI respectively) while slightly larger deviations (2.9% and 2.7% respectively) were obtained when using 12 positions. For both 18- and 12-position sequences these deviations due to sampling were much smaller than those induced by noise (mean deviation of 6.5% and 8.6% respectively). Given an associated total overhead for bed movement of half a minute (18 positions) or 20 seconds (12 positions), G-SPECT-I can be a clinical platform that brings new protocols for fast (dynamic) whole brain SPECT and motion correction into reach.

## 1. Introduction

Brain SPECT with <sup>99m</sup>Tc, e.g. with <sup>99m</sup>Tc-HMPAO or <sup>99m</sup>Tc-ECD, has a widely demonstrated utility in detecting regional cerebral blood flow and in indirectly measuring neuronal activity. This enables the noninvasive assessment of cerebrovascular disease (e.g. stroke) and neurological dysfunction (e.g. epilepsy, dementias) (Juni *et al* 2009, Catafau 2001). In particular, SPECT is the only imaging modality practically capable to perform an ictal scan during epileptic seizures due to the “snapshot” property of the tracers in use (Knowlton 2006, Kim and Mountz 2011). Besides these clinically well-established

applications, additional indications in the psychiatric domain are currently under active evaluation (Camargo 2001, Amen *et al* 2011, Santra and Kumar 2014), for example in post-traumatic stress disorder, anxiety and depression (Amen *et al* 2009, Amen 2015).

Presently general purpose single-, dual- or triple-head SPECT scanners provide a limited spatial resolution of 7 to 10 mm, with sensitivity in the range of ~100–250 cps/MBq. Some dedicated brain SPECT scanners, e.g. CeraSPECT, inSpira HD or NeuroFocus (Stoddart and Stoddart 1992, Fakhri *et al* 2006, Sensakovic *et al* 2014, Stam *et al* 2018), have been developed, but resolutions are still around 7 mm and some are not manufactured anymore. Such a limited resolution hampers detection of small localized perfusion abnormalities which can compromise accuracy of diagnosis and early detection of neuropathology while a low sensitivity requires a relatively high tracer dose and long scanning time resulting in patient discomfort as well as increased risk of motion artefacts. These limited resolution-sensitivity tradeoffs of previous SPECT scanners are due to the conventional collimator designs, a limited number of detectors or restricted detector surface area, lack of image magnification, etc.

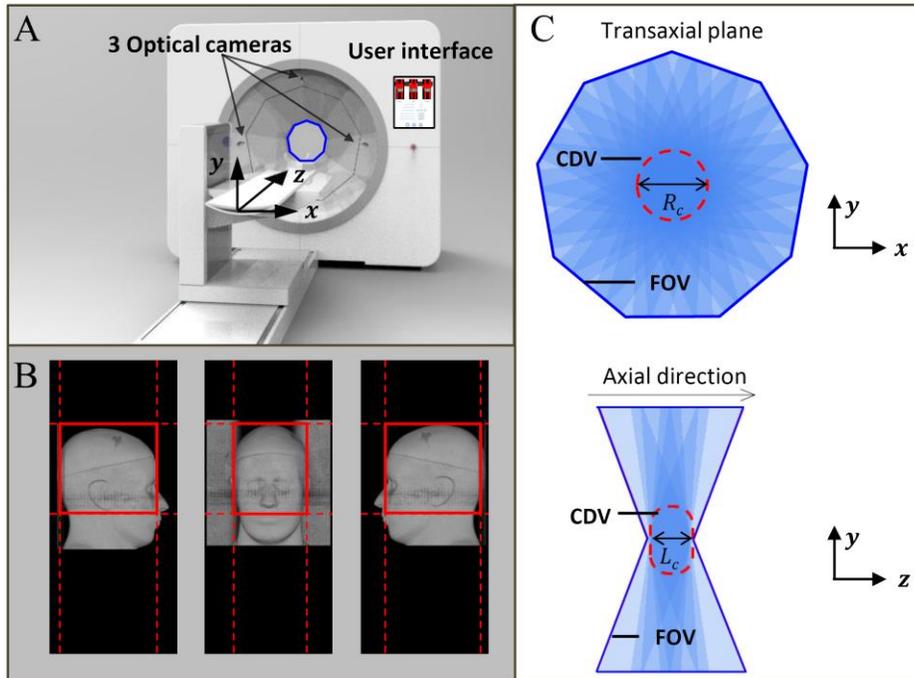
Recently, efforts have been made to develop brain SPECT systems based on multi-pinhole collimation owing to its enhanced resolution-sensitivity tradeoff especially when imaging small objects. Simulation studies have been carried out to optimize multi-pinhole systems (Van Audenhaege *et al* 2011, 2013, King *et al* 2012, Mukherjee *et al* 2014, Chen *et al* 2017), however only a few systems have been built and/or acquired physical scans (Lee *et al* 2014, Beekman *et al* 2015). Our group initially developed various focused multi-pinhole SPECT systems for preclinical purposes, e.g. U-SPECT-I, U-SPECT-II, VECTor, U-SPECT<sup>+</sup> (Beekman 2005, van der Have *et al* 2009, Goorden *et al* 2013, Ivashchenko *et al* 2015), and lately this technology was translated in a prototype system named G-SPECT-I for clinical applications (Beekman *et al* 2015). The preclinical systems achieve sub-half-millimeter SPECT resolution and sub-second-frame dynamic scans for small animals (Befera *et al* 2014, Ivashchenko *et al* 2014, 2015) and are now in use in labs worldwide. The G-SPECT-I system offers an unprecedented resolution down to 2.5 mm and a sensitivity of 415 cps/MBq in scans of human head sized phantoms when a collimator with 3-mm-diameter pinholes is used (Beekman *et al* 2015). These enhanced resolution-sensitivity tradeoffs are facilitated by the systems' design in which all pinholes are focusing on a central volume. This central volume is termed the Complete Data Volume (CDV). For a scan of an object larger than the CDV, the bed is translated in order to extend the volume with ensured sufficient angular sampling. Subsequently, all pinhole projections from all bed positions together are used for image reconstruction of the entire volume using the scanning focus method (Vastenhouw and Beekman 2007).

Recently, we showed that scans of a region which contains a limited number of transaxial slices of the brain (up to 36 mm) can be performed by G-SPECT-I using only 4 bed translations, demanding an estimated overhead time of seconds and thus allowing for very fast dynamic imaging (Chen *et al* 2018). The present paper aims to optimize bed translations of G-SPECT-I for full brain scanning, which is commonly done in brain perfusion studies. To maximize effective sensitivity, scanning speed as well as 4D SPECT frame rate, we investigated (i) confining the axial length to the minimum required, and (ii) limiting the number of bed translations while avoiding truncation artifacts or undersampling, all based on extensive G-SPECT-I simulations including attenuation modeling. Resulting images were assessed both visually and quantitatively.

## 2. Methods

### 2.1. System design

The G-SPECT-I scanner (Fig. 1) consists of nine scintillation gamma detectors each comprised of a  $595 \times 472 \times 9.5 \text{ mm}^3$  NaI(Tl) crystal based cameras, an interchangeable collimator, a precisely controlled xyz-stage for bed translation, three optical cameras and an appropriate user interface for the selection of the scanning volume of interest (VOI) based on the optical cameras (Branderhorst *et al* 2011, Beekman 2011). The collimator assumed in this paper for brain imaging has a total of 54 pinholes (Beekman *et al* 2015). All pinholes are focusing towards the collimator's center, offering a CDV with a transaxial diameter and axial length of 100 mm and 60 mm respectively. Note that for activity in the large volume of the gantry outside the CDV, the emitted photons are still captured by a part of the pinholes (see Fig. 1). Other details concerning the G-SPECT-I system have been explained in (Chen *et al* 2018).



**Figure 1.** Illustration of the G-SPECT-I scanner. (A) G-SPECT-I system with three optical cameras and a user interface for VOI selection; (B) an example of how VOI selection is done with the user interface. The user interface takes the images from three optical cameras as input. (C) The CDV in transaxial view (top image) and along axial direction (bottom image). The CDV is the volume “seen” by all pinholes; it has a transaxial diameter  $R_c$  of 100 mm and an axial length  $L_c$  of 60 mm. The entire field of view (FOV) of the scanner, at one bed position, is much larger than the CDV; it extends over the gantry as shown in the figure.

### 2.2. Simulation set up

A digital Zubal phantom (Zubal *et al* 1994) was used for simulating normal brain perfusion images (Fig. 2). The activity map was generated by segmenting the Zubal phantom into grey matter, white matter and Cerebral Spinal Fluid (CSF) and assigning activity concentrations to these regions with a ratio of 4:1:0 respectively as in (Glick and Soares 1997, R.Z. *et al* 2000, Pato *et al* 2015). We forced the phantom to be

perfectly symmetric by mirroring the phantom left hemisphere to the right. This was to avoid any bias induced by the intrinsic left-right asymmetry of the Zubal phantom during image analysis. This phantom was subsequently interpolated (tri-linearly) in PMOD v4.0 (PMOD Technologies Ltd., Switzerland) from its original size of  $1.1 \times 1.1 \times 1.4 \text{ mm}^3$  to  $0.75 \text{ mm}^3$  voxel size, half the voxel size of the reconstructed image ( $1.5 \text{ mm}^3$ ), to mimic a continuous activity distribution reconstructed on a discrete grid. System matrices for forward projection of the activity distribution and reconstruction were both generated using a set of  $^{99\text{m}}\text{Tc}$  (140 keV) point source measurements and geometrical modeling (van der Have *et al* 2008). To obtain realistic simulated projections, effects of attenuation were included using a voxelized ray tracer (Goorden *et al* 2016, Wang *et al* 2017). Attenuation map were obtained by assigning regions in the Zubal phantom to bone, soft tissue and air with an attenuation coefficient of 0.31, 0.15 and  $0 \text{ cm}^{-1}$  respectively (Fig. 2C). Although attenuation was included in simulating projections, no attenuation correction was performed on the reconstructed images. Similarity regulated OSEM (Vaissier *et al* 2016) with 8 subsets and 10 iterations was performed using the scanning focus method (Vastenhouw and Beekman 2007) to combine all projections from all bed positions simultaneously into image reconstruction.

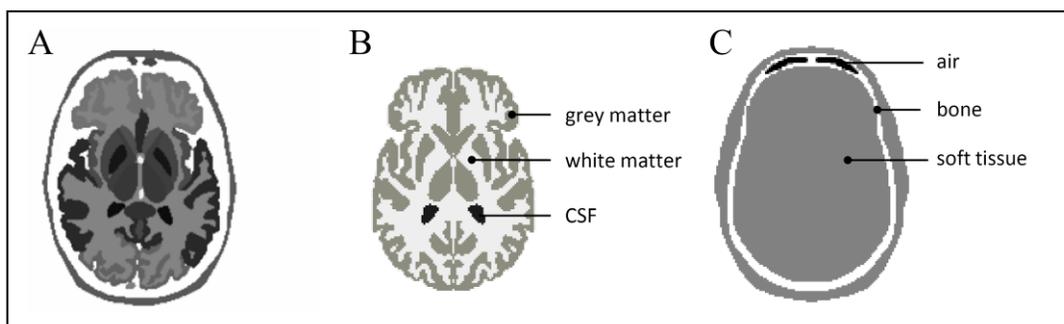


Figure 2. Phantoms used for brain perfusion simulation: (A) the Zubal phantom, (B) activity distribution in phantom, and (C) attenuation map. Tracer concentration in grey matter, white matter and CSF is set to be 4:1:0. Attenuation coefficients assigned to bone, soft tissue and air are 0.31, 0.15 and  $0 \text{ cm}^{-1}$  respectively.

### 2.3. Noise-free simulations for bed sequence optimization

Bed sequence optimization was performed using noise-free simulations to quantify errors solely induced by sampling. Sequences investigated here all follow a multi-planar trajectory, meaning that bed positions in each transaxial plane are replicated along axial direction to extend the scan length. To serve as a reference, we first simulated an oversampled full brain scan obtained by i) scanning the full axial length of the brain; ii) keeping a small separation (compared to the 60 mm length of the CDV) of 21 mm between consecutive axial positions; and iii) using a large number of 16 bed positions in each transaxial plane. This reference scan thus employs a total number of 128 small bed translations (8 axial and 16 transaxial positions).

Subsequently, to optimize the bed translation path, a series of scans using a reduced number of bed positions were simulated and compared to the reference scan. This optimization was done according to the following three steps (see also Fig. 3).

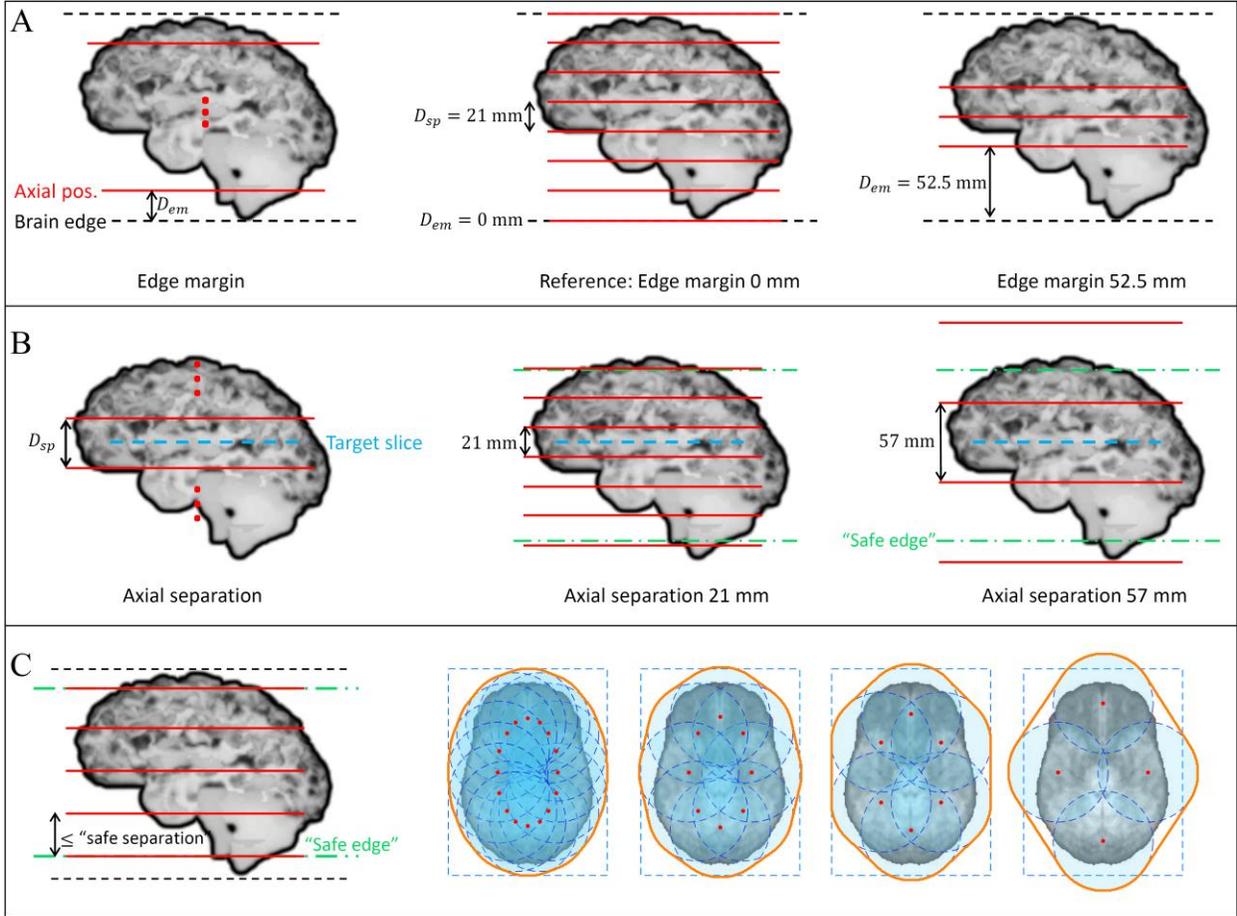


Figure 3. Illustration of the bed sequence optimization for (A) edge margin  $D_{em}$ , (B) axial separation  $D_{sp}$ , and (C) number of transaxial bed positions  $N_{tr}$ . The brain image shown represents a maximum intensity projection of the brain perfusion phantom in the coronal view. In (A), oversampling in the brain between the first and last sampling planes is always ensured by using a safe  $D_{sp}$  of 21 mm and a  $N_{tr}$  of 16. In (B), bed positions are added until at least the “safe” edge found in step (A). In (C) the left figure illustrates the final axial position placement, based on the results of the optimal  $D_{em}$  and  $D_{sp}$ . With this axial placement, sampling sequences with a  $N_{tr}$  of 16, 8, 6 and 4 are tested which are displayed at the right. The red dots highlight the transaxial bed positions, and the blue circles indicate the outer contours of the CDVs. The dashed blue box denotes the selected VOI on the transaxial plane. The convex hull of the CDVs, in which complete data is obtained, is represented by the orange line.

- 1) Confine the axial scan length by searching the maximum allowed edge margin  $D_{em}$  that still allows for artifact-free whole brain imaging.
- 2) Maximize the separation  $D_{sp}$  between consecutive axial positions to facilitate a minimum number of axial positions.
- 3) Further minimize the required number of transaxial positions per plane  $N_{tr}$ , using the optimal settings found in the previous steps.

Each step is explained in detail in the subsections below.

### 2.3.1 Axial edge margin $D_{em}$

To find the maximum “safe” edge margin  $D_{em}$ , we gradually increased  $D_{em}$  from 0 mm (reference scan) to 10.5 mm, 21 mm, 31.5 mm, 42 mm, 52.5 mm (as shown in Fig. 3A which illustrates the two extreme cases). Oversampling in the region between the first and last sampling plane was always ensured by using a small  $D_{sp}$  of 21 mm and 16 bed positions in the transaxial plane, the same settings as used for the reference scan.

### 2.3.2 Axial separation between consecutive positions $D_{sp}$

The optimal axial separation was investigated by gradually increasing the value of  $D_{sp}$  from 21 mm up to 60 mm (the length of the CDV). To have a fair comparison among scans with different  $D_{sp}$ , a target slice was adopted, around which axial positions were placed symmetrically (see Fig. 3B). Here the value of  $D_{sp}$  was set to be 21 mm, 30 mm, 39 mm, 48 mm and 57 mm (increasing at a multiple of  $2 \times 1.5$  mm for the symmetric placement). The target slice was placed at the center of the thalamus, which contains rich perfusion patterns and involves multiple important subcortical structures (e.g. caudate, putamen). We regard this slice to be the most “problematic” for all sequences since it locates exactly in between two sampling planes in all cases. Meanwhile, for all scans with different axial separations it was ensured that the axial length was sufficiently long. In principle, this could be accomplished by placing the first/last axial position at a common top/bottom edge margin (e.g. all at the “safe edge” found in the previous step) and adding axial positions in between. However, this greatly limits the choice for  $D_{sp}$ . Therefore, in this study axial bed positions with a designated separation were added until *at least* the “safe” edge margin (Fig. 3B).

### 2.3.3 Transaxial positions $N_{tr}$

The findings in the aforementioned axial placement step were used as a starting point to further optimize sequence design in the transaxial plane. We kept  $D_{em}$  at the maximum “safe” edge margin while making sure that  $D_{sp}$  was not larger than the “safe” axial separation (see Fig. 3C) and we gradually decreased the number of transaxial positions. The design of all transaxial bed sequences was based on the previously proposed protocol described in (Chen *et al* 2018), which assumes that a VOI is selected in the transaxial plane based on the subject’s head contour which could be done using the G-SPECT-I user interface (Fig 1B). A sequence was then designed based on the selected VOI and a transaxial data-completeness model which ensures sampling sufficiency in the convex hull surrounding the CDVs (Chen *et al* 2018). An illustration of the designed transaxial sequences for a G-SPECT-I brain perfusion scan based on this protocol is displayed in figure 3C; from an oversampled sequence using 16 bed positions per transaxial plane, to sequences using 8, 6 and 4 bed positions per plane.

## 2.4. Noisy simulations

To place the sampling-induced deviations in the context of image variations due to statistical uncertainty caused by the limited number of detected photons, we additionally performed reconstructions with noisy projection data (for 20 Poisson noise realizations based on the noiseless projections). This was done for the reference sequence as well as for a selected number of sequences with reduced number of bed positions. These noisy simulations assumed a total of 50 MBq of  $^{99m}\text{Tc}$  in the brain (Laere et al 2000, Nobili et al 2002, Bowen et al 2011) and were representative for a scan time of 30 min.

## 2.5. Evaluation

Assessment of the simulated perfusion scans was performed by visual inspection and quantitative Region of Interest (ROI) analysis. The latter was achieved by calculating the Brain Uptake Ratio (BUR) and the Asymmetry Index (AI) in selected ROIs. These two metrics are given by

$$BUR = \frac{C_{target}}{C_{background}} \quad (1)$$

$$AI = \frac{C_{R-target} - C_{L-target}}{C_{R-target} + C_{L-target}} \times 200\% \quad (2)$$

Here  $C_{target}$  and  $C_{background}$  denote the mean uptake value in the target and background ROI respectively. In this work the entire cerebellum (Fig. 4F) directly segmented from the Zubal phantom was used as the background region. The mean uptake value  $C_{R-target}$  is the measurement from the ROI in the right hemisphere while  $C_{L-target}$  is that of the corresponding ROI in the left hemisphere.

Varied ways of target ROI definition are used for perfusion SPECT assessment across studies. One of the common approaches entails manually delineating ROIs in the four big lobes (i.e. frontal, temporal, parietal and occipital lobe), sub-regions of the lobes (e.g. inferior and superior frontal lobe, lateral and medial temporal lobe, etc.), and/or in subcortical structures (e.g. cingulate, thalamus, etc.) (Charpentier *et al* 2000, Tsolaki *et al* 2001, Staffen *et al* 2006, McNeill *et al* 2007, Colloby *et al* 2010). Besides, automated methods -which could reduce labor and variability compared to manual ROI placements- are often performed by registering subject scans to a template (e.g. an averaged scan from databases) or an atlas (e.g. Talairach atlas). However, this generally requires subject MR scans, templates with already segmented ROIs, etc., while displacement due to misregistration, possibly a few mm (Grova *et al* 2001, Radau *et al* 2001), could bring bias/errors for quantification on the simulated high resolution images. In addition, some studies implement “polar maps” to generate ROIs by simple image processing on subject SPECT scans. The polar map delineates regions along the periphery of the brain in the transaxial plane covering most of the grey matter, where manually drawn ROIs are often placed. The latter approach of ROI definition was implemented in our work. Meanwhile, we also incorporated some ROIs from subcortical structures and in the coronal plane to make the measurement more comprehensive as they have also been used in literature (Tsolaki *et al* 2001, Colloby *et al* 2010).

A total number of 51 target ROIs was used (see Fig. 4), among which 36 ROIs were placed in three transaxial planes, 9 ROIs in two coronal planes and 6 subcortical ROIs (caudate, putamen and thalamus in both hemispheres) were directly segmented from the 3D Zubal phantom. For the transaxial slices, an

inferior (Fig. 4A) and a superior (Fig. 4C) slice were placed at the center of the thalamus and tangential to the cingulate respectively, as in (Cutolo *et al* 2000, Chiu *et al* 2001). A middle slice (Fig. 4B) was chosen to be the slice exactly in between the two. To generate the polar map regions on the transaxial slice, an annulus region was obtained by segmenting the brain outer boundary from the digital phantom and extending it from the outer boundary inwards for 15 mm, as in (Mountz *et al* 1995, Deutsch *et al* 1997). This annulus was subsequently divided into 12 equal angular sectors. For ROIs in the coronal plane, the orbital and dorsolateral part of the frontal lobe and cingulate (Fig. 4D), as well as the mesial and lateral part of the temporal lobe (Fig. 4E) were considered, as in (Chiu *et al* 2001). These transaxial and coronal ROIs have a size in the range of 0.4–1.0 cm<sup>3</sup> with a mean value of 0.8 cm<sup>3</sup>. The subcortical ROIs (as displayed in Fig. 4A on one transaxial slice) vary in size from 4.4–5.7 cm<sup>3</sup>. Figure 4F illustrates the location of the selected transaxial and coronal planes as well as the cerebellum in the brain.

For each simulated scan, its BUR and AI values in all 51 ROIs were calculated and compared to those from the (noise-free) reference scan. We assessed the magnitude of the deviations from this reference scan when scanning with various bed sequences. These deviations are defined as:

$$Dev BUR = \frac{|BUR - BUR_{ref}|}{BUR_{ref}} \times 100\% \quad (3)$$

$$Dev AI = |AI - AI_{ref}| \quad (4)$$

Here *Dev* stand for the deviation from the reference scan, while  $BUR_{ref}$  and  $AI_{ref}$  are the BUR and AI values of the reference. The deviation of AI is calculated directly by subtracting the  $AI_{ref}$ , since AI is already a normalized index expressed in percentage. Note that the BURs are always positive (Eq. 1) and AIs here could be either positive or negative (Eq. 2).

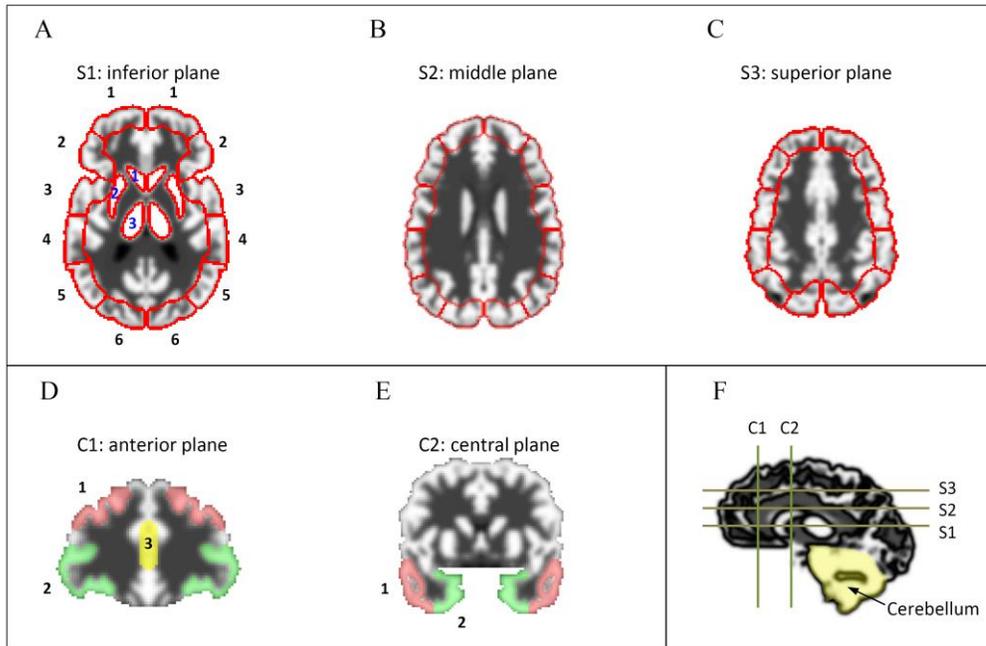


Figure 4: Illustration of the 51 target ROIs for quantitative analysis. Panels A-C show ROIs in three transaxial slices. Panels D-E display the ROIs in two coronal slices. Panel F indicates the location of the selected transaxial or coronal slices in the brain. In each transaxial slice, 12 peripheral ROIs are segmented symmetrically on the left and right hemisphere. The subcortical regions in the inferior plane are depicted in panel A

For all images presented in this paper, the noise-free scans were post filtered with a 3D Gaussian filter of 4 mm full width at half maximum (FWHM) and displayed with a slice thickness of 1.5 mm. The noisy scans were 6-mm-FWHM Gaussian filtered and displayed with a larger slice thickness of 6 mm to suppress small local fluctuations due to noise. For quantitative analysis of all scans, measurements were performed on the unfiltered images to avoid any bias from filtering. Additionally, we included some quantitative results obtained from 6-mm-FWHM Gaussian filtered images for a selected number of scans, since quantification of clinical SPECT is commonly performed on filtered images.

### 3. Results

#### 3.1. Noise-free simulations

##### 3.1.1 Axial edge margin $D_{em}$

Figure 5A shows the sagittal view of simulated perfusion images with an increasing edge margin  $D_{em}$ . The red lines indicate the locations of the first/last axial bed positions while the dotted white lines denote the upper/bottom edge of the brain. Compared to the reference scan (with  $D_{em} = 0$  mm), scans with a  $D_{em}$  up to 31.5 mm appear hardly degraded upon visual inspection while further increasing  $D_{em}$  to 42 mm or 52.5 mm results in some artefacts at the edges of the brain. For an additional check, a top and a bottom transaxial slice are selected and displayed in figure 5B. Image profiles on these two transaxial slices are displayed in figure 5C. Figure 5B and 5C confirm the sufficient coverage of the brain for scans with a maximum  $D_{em}$  of 31.5 mm as structures in the top or bottom transaxial slices are well preserved compared to the reference scan.

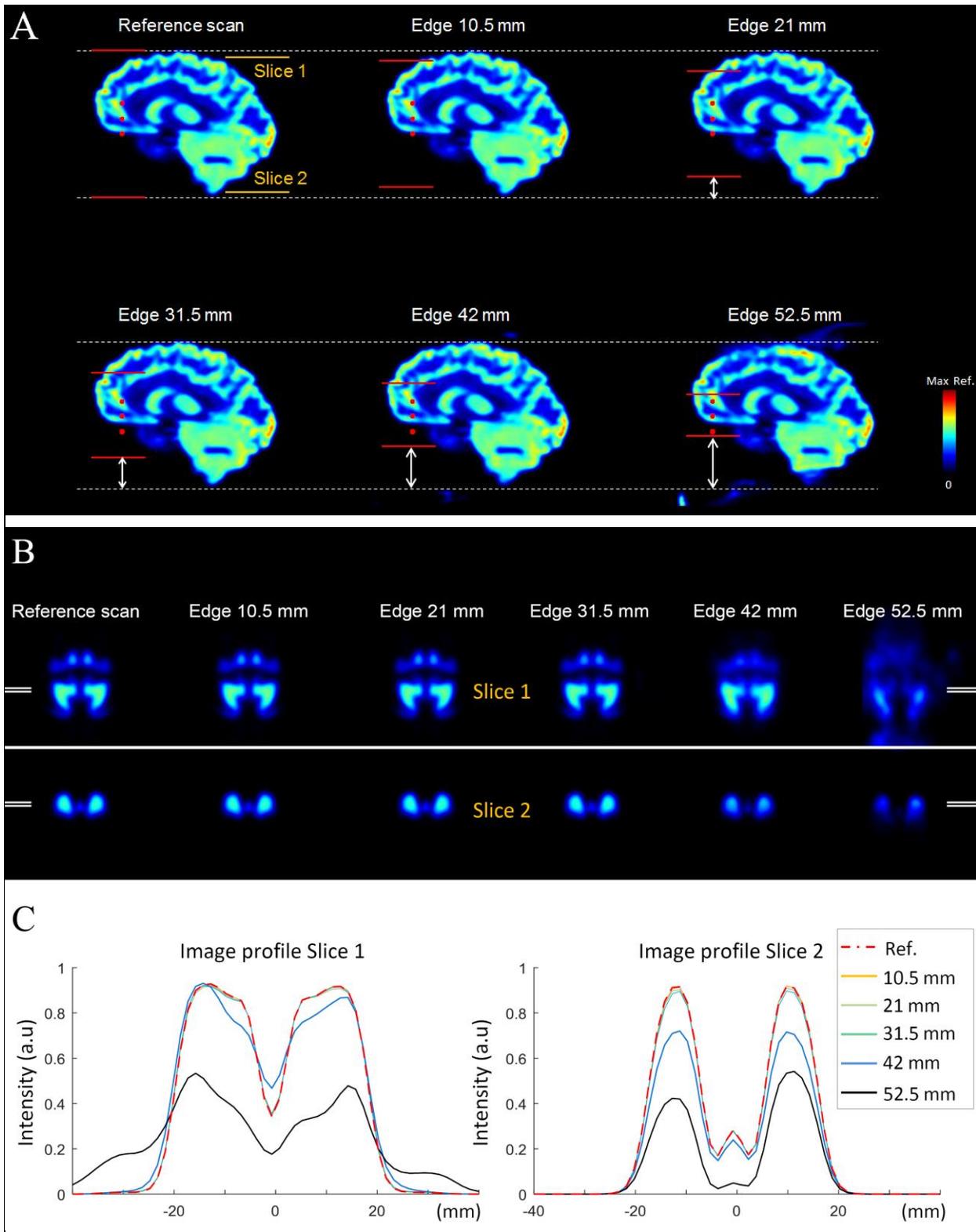


Figure 5 Comparison of scans with different edge margin  $D_{em}$ . (A) Simulated sagittal image slices are displayed. The red lines indicate the locations of the first/last axial bed positions and the dotted white lines denote the upper/lower edge of the brain. The same colormap ranging from 0 to the maximum intensity of the reference scan is used for all simulated perfusion images in this paper. (B) A top and bottom transaxial slice are displayed. The locations of these two slices are indicated in panel A. Image

profiles through each transaxial slice are included and shown in panel C. These profiles are taken from a line with a width and thickness of 4.5 mm.

### *3.1.2 Axial separation $D_{sp}$ between consecutive sampling planes*

To compare the scans with different  $D_{sp}$ , the target slice (which always locates exactly in between two sampling planes) as well as image profiles are shown in figure 6A and 6B respectively for all sequences. Figure 6 shows that visual differences between the simulated images acquired with varied values of  $D_{sp}$  are small; patterns are well preserved with no obvious distortions even for a value of  $D_{sp}$  of 57 mm. This is further confirmed by the coronal view comparison in figure A1 in the appendix.

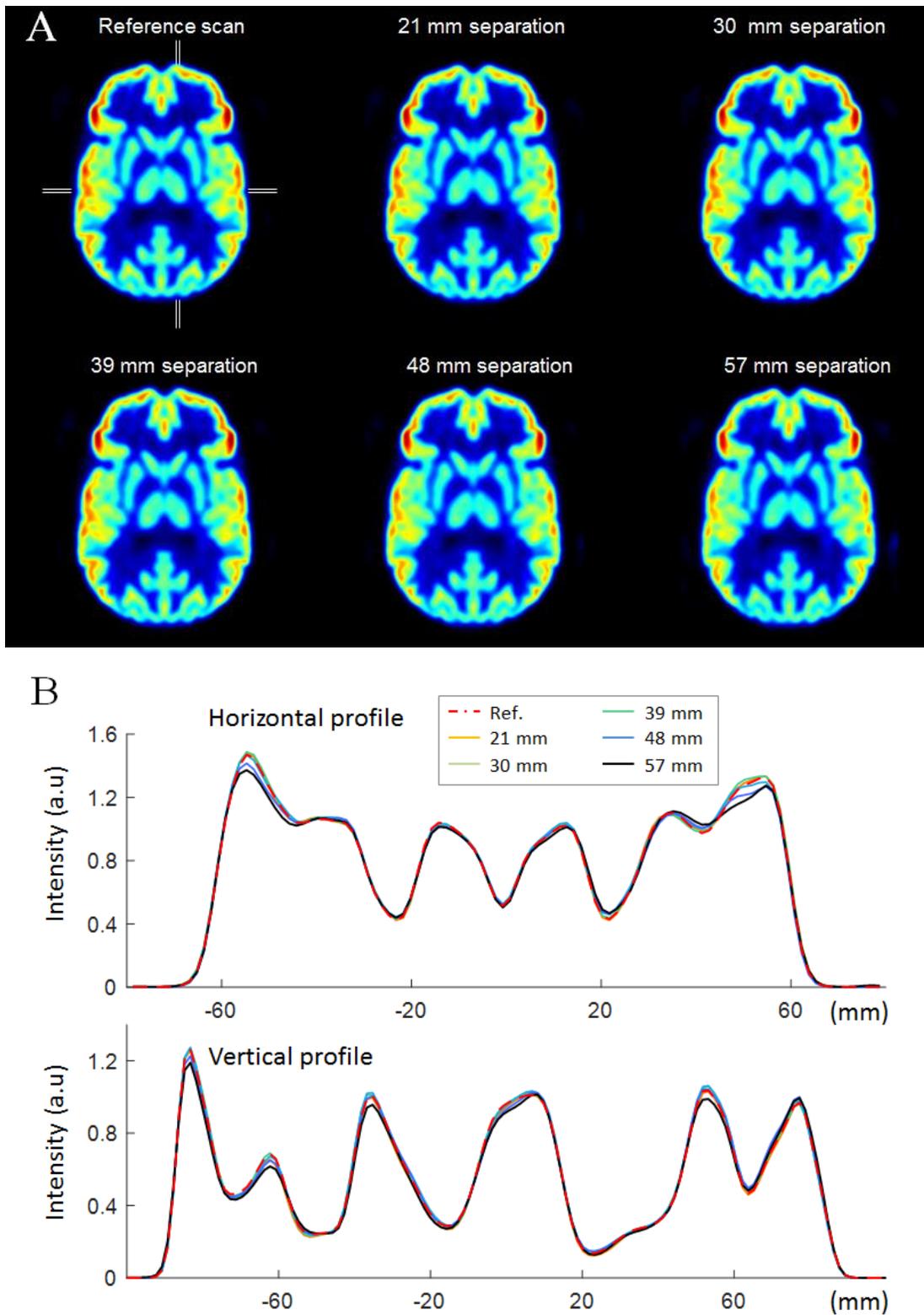


Figure 6 Comparison of the target slice for scans with different axial separations. (A) The target slice is displayed for different scan sequences. (B) A horizontal and a vertical image profile through the target slice are shown. These profiles are taken from a line with a width and thickness of 4.5 mm. Note that the reference scan is simulated using an axial separation of 21 mm and covers the entire brain using 8 axial positions (see Fig. 3A), while the middle image on the first row of panel A (21 mm

separation) is simulated with an axial separation of 21 mm and sufficient axial bed positions (5 in this case) are added to reach the safe edge margin of 31.5 mm.

To quantitatively assess the effect of increasing  $D_{sp}$ , we calculated brain uptake ratio BUR for the 12 polar map regions on the target slice (Fig. 7A). Compared to the reference image, scanning with an increased value of  $D_{sp}$  up to 57 mm achieves comparable BUR measurements (maximal deviation of 6.0% from the reference) among all selected ROIs on the target slice.

Besides a direct comparison of the BURs on the target slice, deviations from the reference scan among all 51 ROIs in the entire brain are calculated and displayed in figure 7B. Due to the large number of ROIs assessed, only the maximum and mean deviation from all ROIs are plotted. Figure 7B demonstrates that deviations from the reference for the tested scans acquired with different  $D_{sp}$  are all below 7%. For the scan with a  $D_{sp}$  of 48 mm, the BUR and AI deviate maximally 5.0% and 3.2% respectively, while the mean deviations read only 1.3% and 0.8%. Based on these visual and quantitative results (Fig. 6–7), a maximum axial separation  $D_{sp}$  of 48 mm is used for further transaxial sequence optimization.

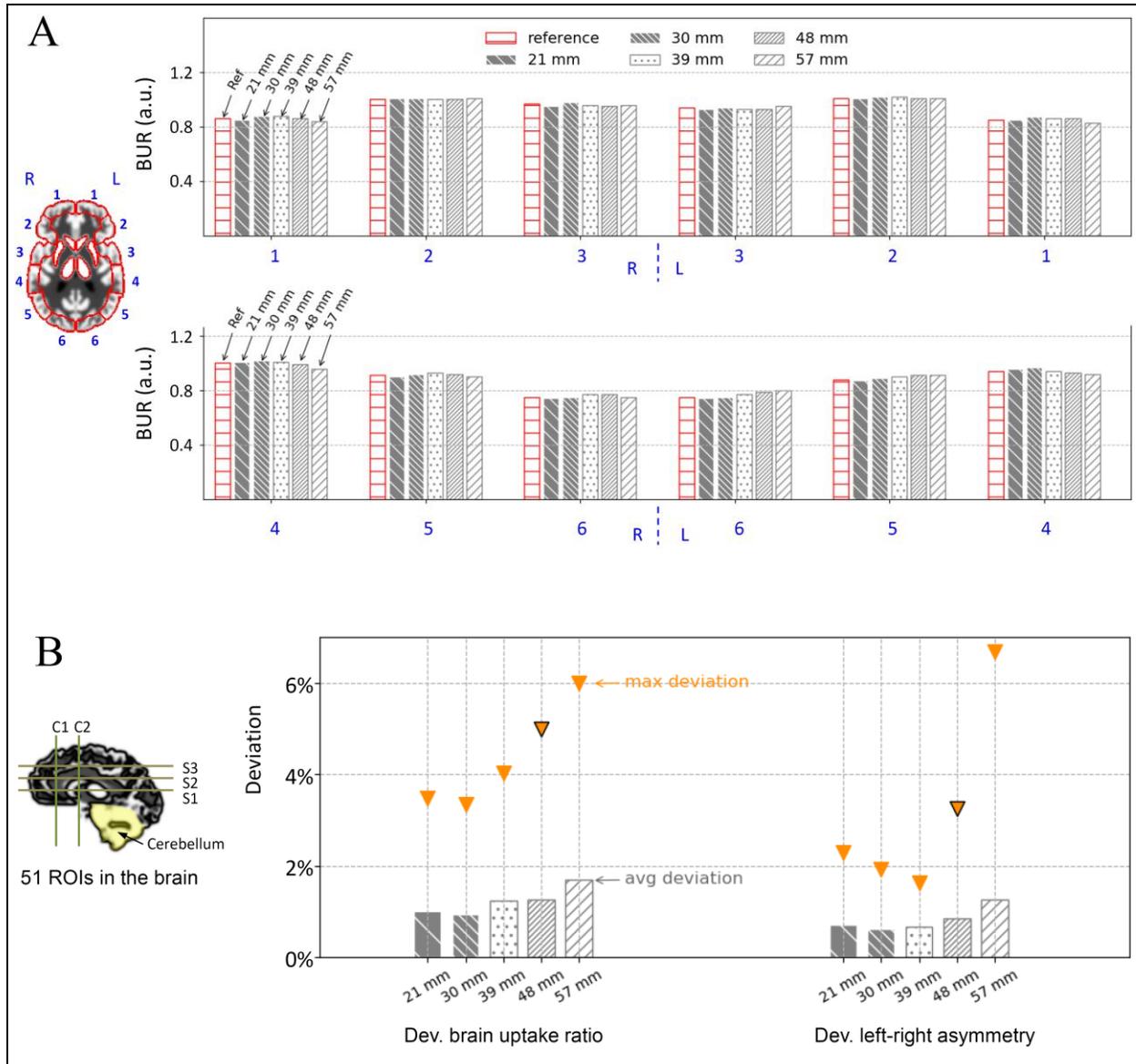


Figure 7. Comparison of the BUR and AI measurements between the reference and scans with an increased axial separation  $D_{sp}$ . (A) Direct comparison of the BURs for the tested sequences in ROIs on the target slice; (B) deviations from the reference of the BUR and AI among all 51 ROIs (see Fig. 4) in the entire brain. The maximum and average deviation are shown with a triangle and a bar respectively.

### 3.1.3 Transaxial sampling sequence

Figure 8 shows a comparison of scans with different numbers of transaxial bed positions  $N_{tr}$ . All scans (except the oversampled reference) use the same axial bed position placement (Fig. 8A) based on the previous results (optimal  $D_{em}$  and  $D_{sp}$ ) and adjusted to the size of Zubal phantom; we keep  $D_{em}$  to be 31.5 mm while adding axial positions such that  $D_{sp}$  is not larger than 48 mm (42 mm here). Figure 8A shows two transaxial slices which are both in between two sampling planes, while figure 8B gives a

comprehensive comparison of the transaxial images from the top to the bottom of the brain. Additionally, as other views are also important for perfusion scan assessment, we include more image comparisons for the coronal view in the appendix (Fig. A2). Both the transaxial and coronal view results show that reducing the number of bed positions from the oversampled reference scan to 18 (3 axial positions combined with 6 transaxial positions) hardly has a visual effect on perfusion images. Further decreasing the number of transaxial bed positions to 4 leads to relatively larger deviations from the reference as well as a slightly degraded left-right symmetry.

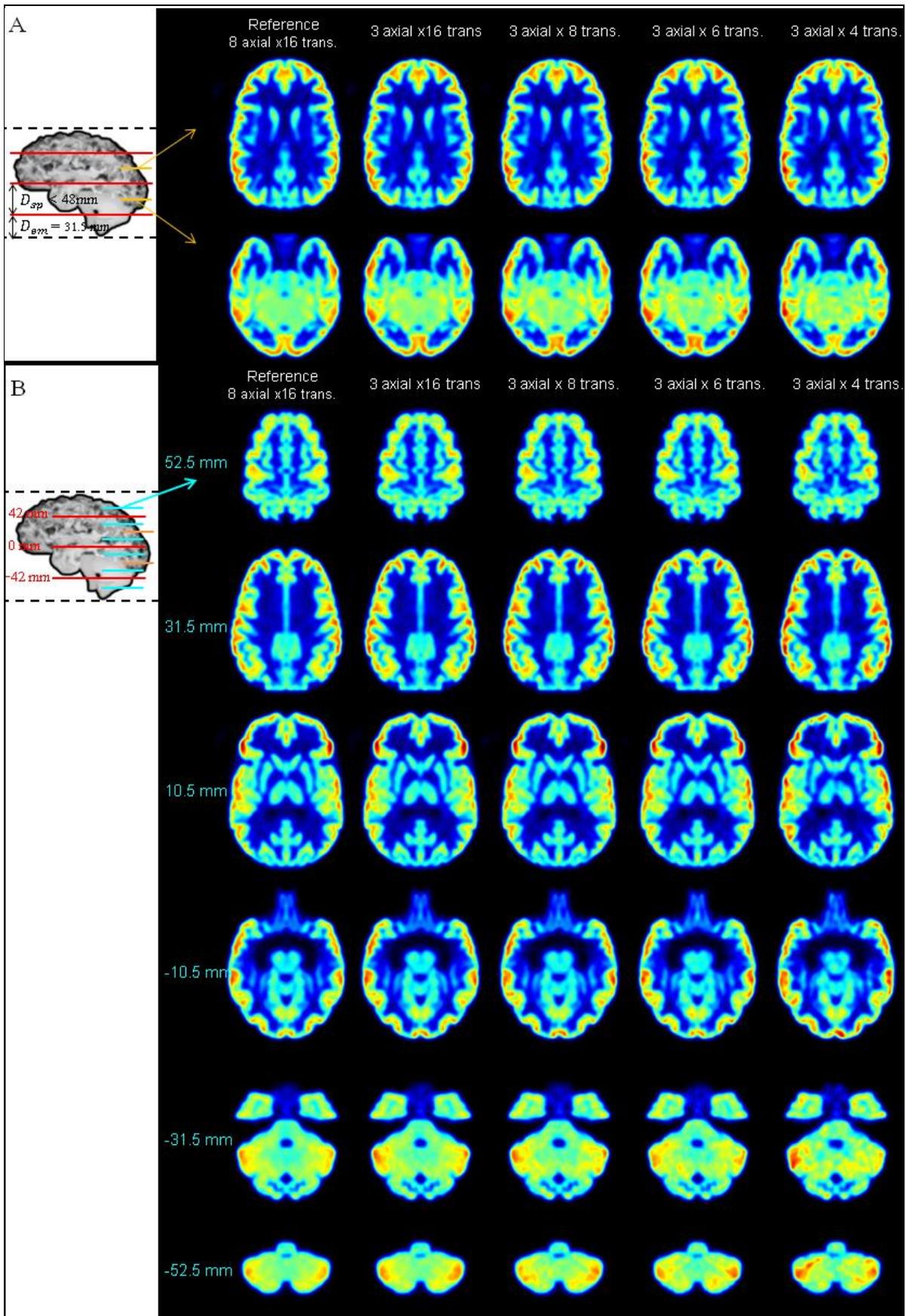
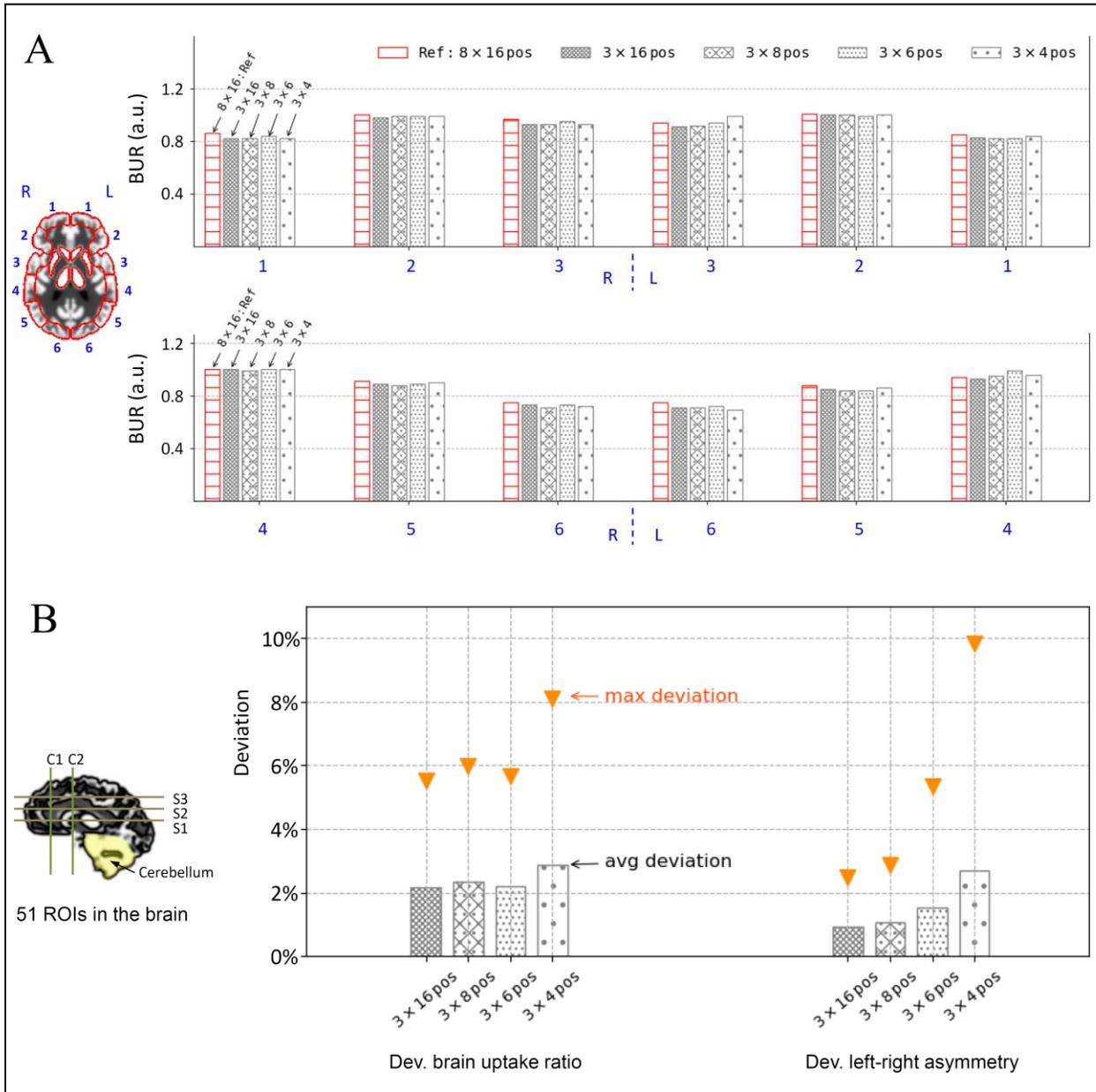


Figure 8 Comparison between the reference scan and scans with different transaxial bed positions. (A) Two transaxial slices which are both exactly in between two sampling planes; (B) transaxial slices from top to the bottom of the brain.

A quantitative analysis is included in figure 9 which shows a direct comparison of the BURs for the 12 polar map ROIs on the target slice (Fig. 9A), as well as the maximum and average deviations in BUR and AI from the reference among all 51 ROIs (Fig. 9B). For all the tested transaxial sequences, these deviations are below 9.8%. When using 6 transaxial positions with the proposed axial placement, the maximum deviation of the two measurements are 5.7% and 5.4% for BUR and AI respectively, while the mean deviations read only 2.2% and 1.5%. Further decreasing the number of transaxial positions to 4 leads to a maximum deviation of 8.1% and 9.8% for the BUR and AI respectively, and a mean deviation of 2.9% and 2.7% respectively.



### 3.2. Noisy simulations

Noisy simulations were performed for the reference sequence (Noisy-ref) as well as for two selected sequences based on the results above, i.e. the sequence with 18 (Noisy-18: 3 x 6 positions) and 12 positions (Noisy-12: 3 x 4 positions). Examples of the simulated noisy images are shown in Figure 10A.

Quantitative assessment of the BUR and AI deviations from the (noise-free) reference scan are provided in Figure 10B. This figure shows that deviations due to Poisson noise are 3–4 times larger than those induced by sampling; for example, reducing the number of bed positions to 18 or 12 positions leads to a mean (BUR or AI) deviation from the reference in the range of only 1.5%–2.9% when assessed on unfiltered images, while these two mean deviations (BUR and AI) for Noisy-ref are 6.5% and 8.6% respectively. Using a post filter (6-mm-FWHM Gaussian) either on noise-free or noisy scans could reduce the quantification error typically by a factor of 1.5 to 2. For example, the sampling induced BUR or AI deviations (with 18 or 12 positions) decrease to mean values of 0.7%–1.9% when images are filtered, while for the Noisy-ref scans the mean deviation decreases to 4.2% and 2.5% for BUR and AI respectively.

Compared to Noisy-ref, Noisy-18 achieves a slightly better performance, which could be explained by the increased count yield (1.2 times higher for the more focused 18-position sequence than for the reference sequence). Noisy-12 obtains a similar quantitative accuracy as Noisy-ref for unfiltered images, but slightly larger deviations (0.7% and 0.6% larger mean deviations for BUR and AI respectively) when assessed on the filtered scans.

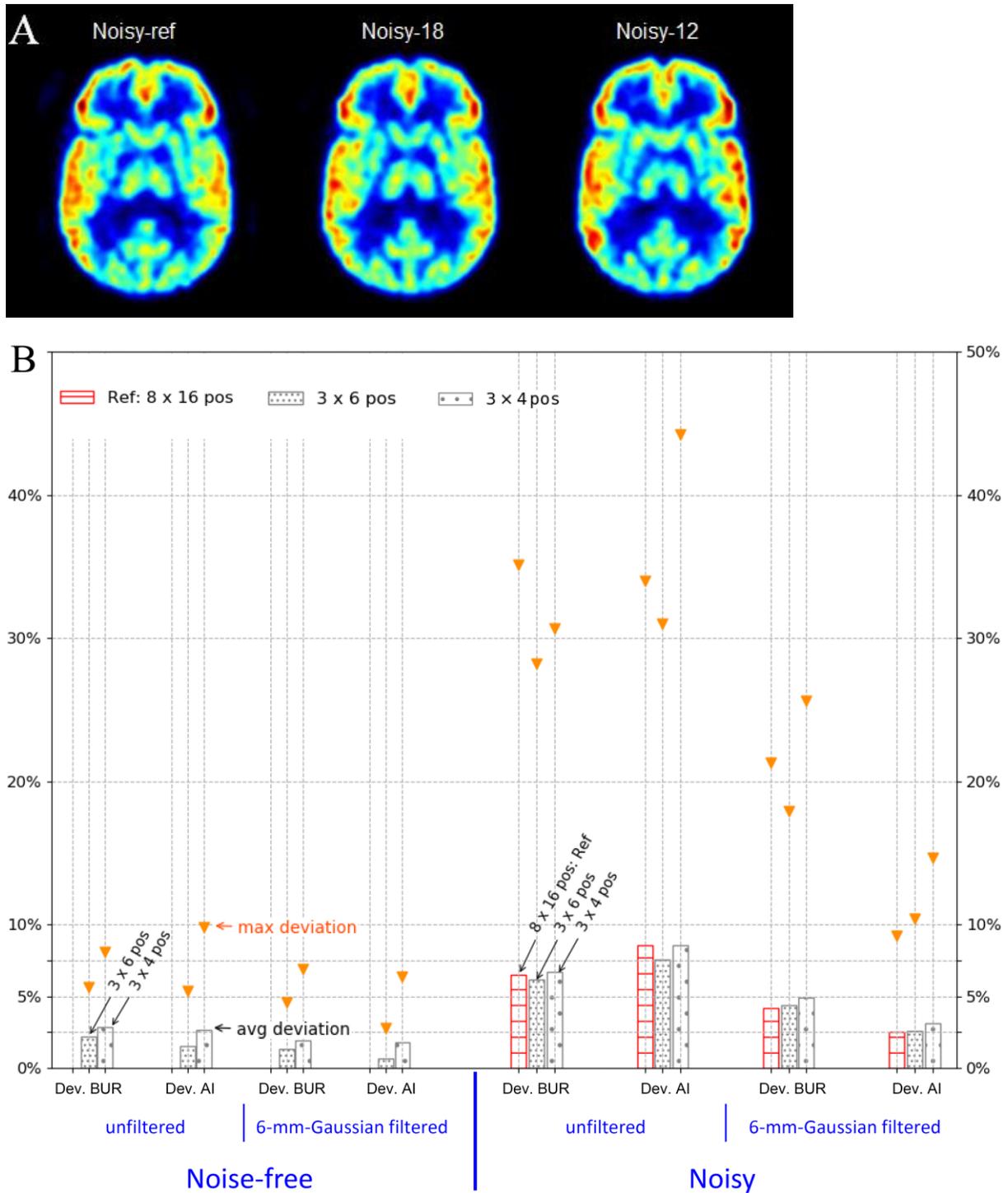


Figure 10. Comparison of the noisy simulations for the reference sequence (Noisy-ref) as well as for sequences with 18 (Noisy-18) and 12 positions (Noisy-12). Example of the simulated noisy scans are shown in panel A. Panel B shows the deviations from the (noise-free) reference scan for the noiseless and noisy unfiltered scans and for these scans applying a Gaussian filter of 6 mm FWHM. The maximum and mean deviation are shown with a triangle and a bar respectively. For the noisy simulations, the maximum and mean deviations were calculated from 51 ROIs and for all 20 noise realizations.

#### 4. Discussion

A big challenge in clinical brain imaging is to achieve an excellent resolution-sensitivity tradeoff that allows for visualization of small lesions at a reasonable radiation dose, while fast (dynamic) capabilities that can be used in motion correction are advantageous as well. Previously we have demonstrated excellent resolution-sensitivity tradeoff of the G-SPECT-I scanner in physical phantom scans (Beekman *et al* 2015). The current work presents G-SPECT-I acquisition using a limited number of bed translations that still allows artifact-free high resolution whole brain scanning. We estimated the total overhead time of 18 and 12 positions to be only 30 and 20 seconds respectively (based on estimations involving the current G-SPECT-I prototype). This may enable fast dynamic studies and multi-frame scans for motion correction.

Note that with G-SPECT-I, overhead time is introduced by the bed translations required to scan volumes larger than the CDV, while for traditional SPECT overhead time is associated with the need to rotate the heads. For traditional scanners with step-and-shoot mode, 64 or 128 views are generally required for sufficient angular sampling (even for a small scanning volume), which results in more than 20 detector stops even for a triple-head system leading to an overhead time of 40-80 seconds assuming 2-4 seconds movement time per view, as reported in (Cao *et al* 1996, Mohseni *et al* 2018). Instead, the G-SPECT-I design with stationary detectors offers the flexibility of performing focused scans where only few bed translations are required while also allowing for extended volume scans.

Effects of attenuation were included in the simulation to make results more realistic. No attenuation correction was performed in the reconstruction for multiple reasons. Firstly, we have not yet determined the attenuation correction method (e.g. transmission imaging based, MR based using deep learning, solely SPECT based, etc.) to be applied in future G-SPECT-I studies. This is currently under development (Chen *et al* 2019), however further testing and validation is necessary. Besides, there are clinicians do not use it (Modzelewski *et al* 2012), possibly because it can be prone to errors due to small shifts between SPECT and CT (Larsson *et al* 2003, Bateman and Cullom 2005) or because of the limited accuracy of a contour based uniform attenuation. Therefore we felt it was better to prevent mixing of the sampling issues with attenuation correction inaccuracies due to the use of a not fully validated approach for G-SPECT-I at this stage.

In this paper, we firstly performed noise-free simulations to constrain the analysis to sampling problems associated with different sequences, while later noisy simulations were included to investigate the utility of the optimized sequences in realistic noisy situations. The former step demonstrated that reconstructed images were barely affected (both visually and quantitatively) when the number of bed translations was decreased from 128 down to 18; when further decreasing the number of translations to 12, a somewhat larger deterioration from the reference scan (maximum deviation of 9.8%, see Fig. 9) and some visual deviations (see Fig. 8) were observed. This maximum deviation with the use of a 12-position sequence decreases to 6.9% when quantifications were done on 6-mm-FWHM Gaussian filtered scans (Fig. 10B). In addition, the noisy simulations showed that in the presence of noise, the deviations due to using 18-position or 12-position sequences are almost negligible (3–4 times smaller) compare to those induced by noise. Note that in the noisy simulations bed movement overhead time was neglected as it highly depends on the number of frames in data acquisition and the bed in use. Thus in practical SPECT

scans when overhead time is playing a role, especially in multi-frames studies, one would expect a relatively larger benefit when using sequences with 18 and 12 positions than what is provided in Fig. 10.

For focused scans when only a part of the brain is of interest, the number of bed translations can be further reduced without sacrificing image quality by axially restricting the scan length to just cover the target volume. An example of such an implementation was demonstrated in (Chen *et al* 2018) which presented brain dopamine system imaging with only 4 bed translations. Besides, even for whole brain scans which require very high temporal resolutions, as in brain pharmacokinetic studies (Nakano *et al* 1988, Ogasawara *et al* 2001, Komatani *et al* 2004, Gullberg *et al* 2010), utilizing less than 12 positions remains possible, for example by applying an axial separation  $D_{sp}$  larger than the currently used value of 48 mm. For such fast scans, the effects of noise would be much more prominent than what was shown in figure 10 such that the compromised accuracy due to sampling may be negligible. This could enable imaging tracers with a very short (biological or physical) half-life, such as  $^{133}\text{Xe}$  (biological half-life  $\approx 40$  seconds), for which scanning with a confined axial length, e.g. 71 mm (Knutsson *et al* 2007) is often already done.

Aspects which have not yet been studied here could enable even faster dynamic SPECT imaging. We have assumed the same number of transaxial positions at each axial position; in future work one could study using fewer transaxial positions when scanning parts of the brain with smaller dimensions, e.g. the brain's top and bottom. Besides, strategies that enable a continuous bed motion acquisition would be beneficial as in that case counts would constantly be recorded during the entire scan. Such methods have been proposed for PET imaging with bed translations only in axial direction (Dahlbom *et al* 2001, Brasse *et al* 2002, Casey *et al* 2005). For G-SPECT imaging this requires additional investigations. Moreover, collimators that offer a larger complete data volume are currently under design in our institute. With these developments, one can expect that less or even no bed translations are required, which may help to achieve extremely fast SPECT scans.

## 5. CONCLUSION

We have designed and evaluated different bed position sequences for total brain perfusion imaging with a stationary focusing multi-pinhole SPECT system. We found that decreasing the number of bed positions from 128 representing an oversampled scan down to a small number of 18 or 12 positions has minimal effects on image quantification compared to those induced by noise, while the respective overhead times were estimated to be only 30 and 20 seconds in total. This is important information for developing protocols for fast dynamic brain SPECT and multi-frame scans for motion correction.

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## Appendix

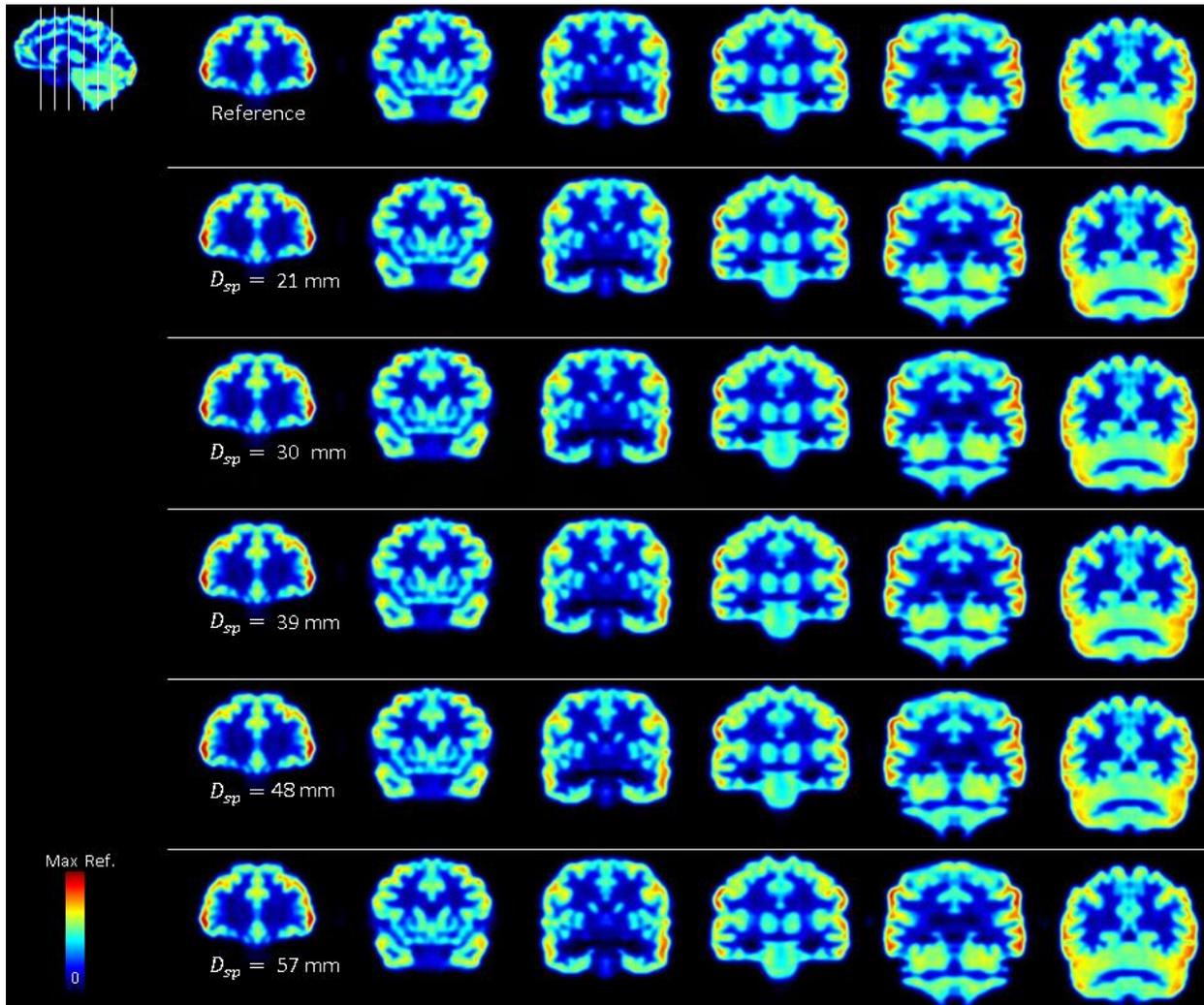


Figure A1. Comparison of simulated perfusion images with the reference image when increasing the axial separation between consecutive sampling planes  $D_{sp}$ . Images are shown in the coronal view. Each row corresponds to one simulated scan, with the  $D_{sp}$  increasing from 21 mm to 57 mm from the 2<sup>nd</sup> row to the bottom row. Images from left to right shows the coronal slices from the anterior of the brain to the posterior. The locations of the slices are indicated in the top left image.

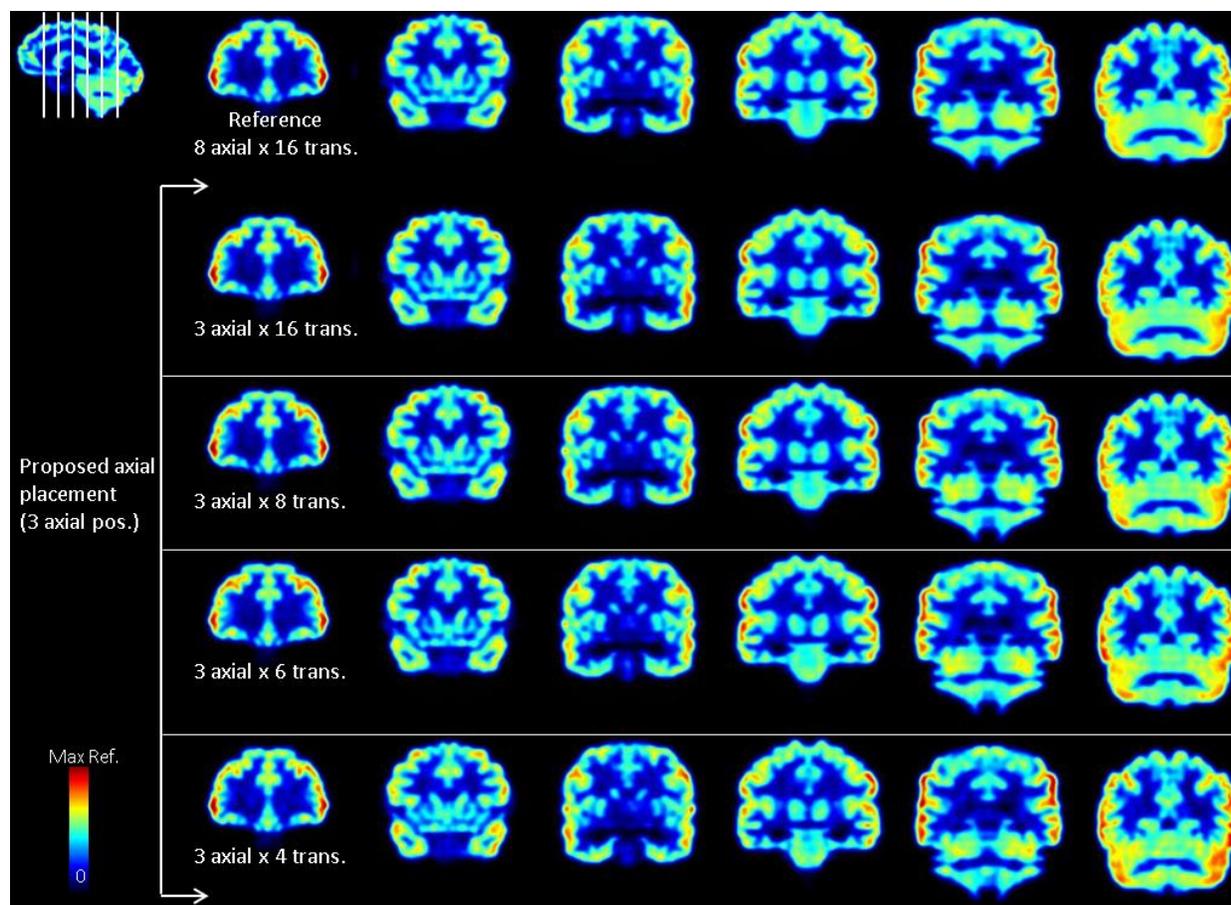


Figure A2. Comparison of simulated perfusion images with the reference image when using the proposed axial position placement but reducing the number of transaxial bed positions  $N_{tr}$ . Each row corresponds to one simulated scan, with the  $N_{tr}$  decreasing from 16 to 4 positions per plane from the 2<sup>nd</sup> row to the bottom row. Images from left to right shows the coronal slices from the anterior of the brain to the posterior. The locations of the slices are indicated in the top left image.

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