Eindverslag van onderzoek "BELSPO Terugkeermandaat" selectiejaar 2011

Title: Novel motion correction techniques for PET imaging of awake animals
Awardee: Jeroen Verhaeghe
Host: Molecular Imaging Center Antwerp (MICA), University of Antwerp

1. Goals

Positron emission computed tomography (PET) is a powerful imaging technique to visualize the interior of an object in a 3D image and has become standard equipment in medical facilities. Recently, scanners dedicated to in vivo pre-clinical small animal imaging applications (microPET or µPET) have been developed. These imaging systems are valuable tools in neurology and oncology (evaluation of disease models, longitudinal evaluation of novel pharmaceutics) amongst others. Recent technological advances have lead to a vast increase in intrinsic spatial resolution of these systems, so much so that motion artifacts become a major resolution-degrading factor in practice. Typically the full resolution potential can only be obtained under ideal conditions in the absence of motion (e.g. post mortem scan versus in vivo scan). In addition, in small animal brain imaging a major factor that limits the translation of results from small-animal studies to humans is the use of anesthesia in small animal imaging as the **anesthesia interfere with many brain processes**. As a result there is an increasing **desire** to scan awake animals. Accordingly, the innovation goal of this project is **to develop and integrate motion correction to state-of-the-art µPET systems to enable molecular imaging of awake small animals for brain imaging.** An optical motion tracking system will be used to track the motion of the animal's head and the motion information will be incorporated into the PET image reconstruction by correcting the sinograms for the measured motion.

2. Methodology

2.1 External motion tracking:

The high temporal resolution requirements of our proposed motion correction scheme necessitate the use of external tracking systems. For the purposes of the project, the Sx60 MicronTracker 3 (Claron Technology Inc.) optical tracking device was purchased. This device tracks specially designed checkerboard-like patterns using a stereo-camera system. The system measures motion (6 degrees of freedom) with at 48 Hz sampling rate and a 0.25 mm accuracy in a field-of-view of 115x70x55 cm (radius x width x height) and is therefore ideally suited to be used together with the Inveon Docked µPET/CT and Inveon µPET (Siemens Preclinical Imaging, TN, USA) scanners available at the Molecular Imaging Center Antwerp (MICA). The set-up of the Inveon Docked µPET/CT at the MICA laboratory is shown in Figure 1 and is comprised of an acquisition laptop that collects and stores the pose measurements (a rotation and translation with 6 degrees of freedom) of the MicronTracker to file, a stereo camera system (2 optical cameras that are horizontally aligned on an axis), a microcontroller to synchronize the PET/CT scanner and the stereo camera, reference checkerboard-like patterns attached to the Inveon µPET scanner that serves to define the optical tracker reference space, a lightweight animal 3D multi-faceted tracking tool with checkerboard-like patterns that is pasted to the animal's head to track the head motion and an external light to illuminate the field-of-view. Because of the small bore size a multi-facet animal-tracking tool was necessary as otherwise the tracking tool could become occluded.

2.2 Alignment and synchronization

The stereo camera records the pose of the tracking tool in a frame of reference that is defined by markers rigidly attached to the PET scanner. To transform these poses to the pose in the PET coordinate system a transformation matrix has to be calculated using a calibration procedure. The calibration has to be performed only once, as long as the reference markers are not moved with respect to the PET scanner, and

can be used with the stereo camera in different positions. For the calibration a [^{18}F]FDG point source is pasted onto the center of origin of a tracking tool and is positioned at several positions in the PET scanner. The point source locations are then determined in the frame of reference of the stereo camera and in the PET images. The transformation matrix is then calculated by minimizing the least squared error between the transformed camera coordinates and the PET coordinates.

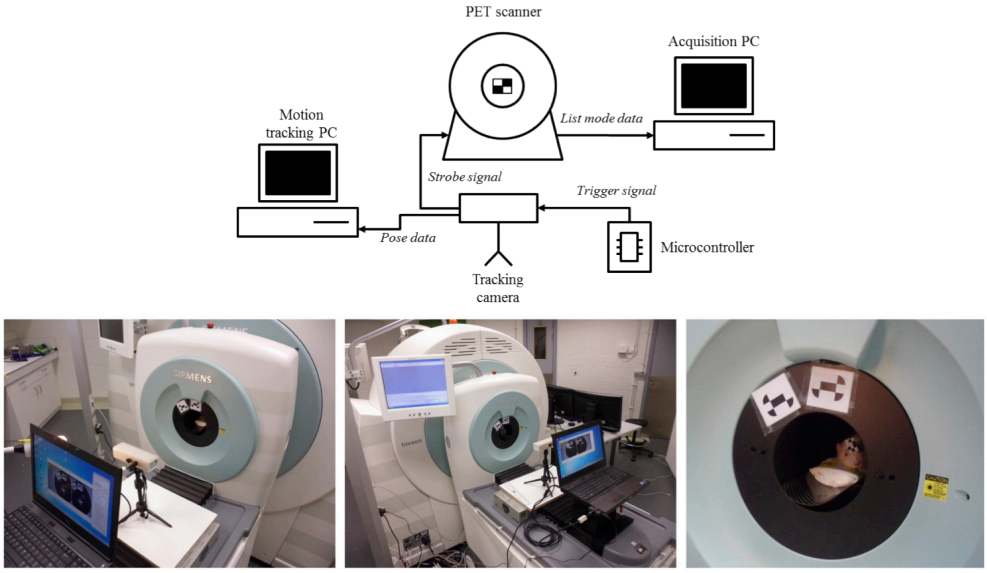

Figure 1 The MicronTracker (ClaronTech) marker based optical motion tracking device and Siemens Inveon Docked µPET/CT scanner at the MICA laboratory (UA).

In order to temporally align the MicronTracker optical tracking system with the Inveon µPET camera an external triggering device based on the Arduino microcontroller environment was developed. The system sends a predefined pattern of trigger signals to the MirconTracker. When the tracking device receives such a triggering signal it records the pose of the tracking tool with respect to the reference frame (within a 10 msec shutter time). At the time the tracking device records a pose, a second trigger is automatically sent to the µPET camera by the tracking device. The µPET records the time at which the trigger is received into the list-mode data stream. Therefore there is a unique link between each pose and each timestamp in the µPET data stream and each PET data event can be linked to a pose, which can then be taken into account for the image reconstruction.

2.3 Sinogram motion correction and image reconstruction

An in-house developed µPET sinogram-binning program that generates motion corrected sinogram data has been developed and validated using computer simulations as part of this project. In particular emission data is acquired in a binary list-mode format available on the Siemens Inveon scanner. This format is a list that stores, for each coincidence detection (i.e. the simultaneous detection of two photons within a 3ns time interval), the energy and crystal positions of both detections along with time tags placed at regular intervals (200µs). After PET acquisition the list-mode file is processed off-line using our in-house developed program that uses the motion information provided by the external tracking system to calculate, for each coincidence event, the instantaneous orientation of the line-of-response (LOR, i.e. the line connecting the two detected events) with respect to the coordinate system fixed to the animal. Finally, the LOR is binned into the Siemens sinogram format using our program. The computational time of this step is proportional to the number of detected coincidence events. In a similar way the normalization correction factors that take into account the motion are calculated. The resulting data will then be

reconstructed using the standard reconstruction programs available on the Inveon scanner. The binning algorithm uses bi-linear interpolation to sample the discrete sinogram bins.

2.4 Phantom experiments

To test the performance of the tracking setup and the sinogram motion correction binning several [^{18}F]FDG phantoms were scanned. The motion could be controlled by pulling strings that were attached to the phantom. The tracking tool was pasted onto the phantom. Several tracking tools, varying in size and pattern, were tested and validated. In an initial experiment, a point source phantom consisting of seven point sources was considered. The point sources were made by soaking molecular sieves in [^{18}F]FDG. In a second set of experiments a hot rod phantom was used. The phantom consists of four 4 cm long capillaries with ultra thin walls placed in a cylindrical holder. The inner diameter of the capillaries is 2, 1.5, 1 and 0.8 mm. The 2 mm capillary was filled with air the other capillaries were filled with [^{18}F]FDG (8.5 MBq/ml). The background in the holder was also filled with [^{18}F]FDG but at a lower concentration (1.5 MBq/ml). One motion free scan (5 minutes) and three scans with motion were performed with scan duration of 25, 15 and 5 minutes and with moderate, low and continuous motion, respectively. A third phantom, a mini Derenzo resolution phantom, consisted of 6 sets of hot rods filled with [^{18}F]FDG in a cold background. The inner diameters of the rods are 1.5, 1.2, 1, 0.9, 0.8, 0.7 mm. These diameters are very challenging for PET imaging, even in the absence of motion, as the resolution of the PET scanner is 1.4 mm.

2.5 Animal experiments

Animals were kept in individually ventilated cages under environmentally controlled conditions and were treated in accordance with the European Ethics Committee (decree 86/609/CEE). All animal experiments were approved by the Animal Experimental Ethical Committee of the University of Antwerp, Antwerp, Belgium (ECD 2011-54).

2.5.1 Awake animal holder and training

To test the behavior of the rats in the enclosed environment of the scanner while wearing the tracking tool, and to develop a practically useful approach to handle the animals during awake scanning, two sets of experiments were considered. One considered a partial constraint approach, in that the animal is placed in a plastic tube (~ 6 cm inner diameter) with an open conic end. The animal was unable to escape through the open end, as its body did not fit through the cone. However, the animal could stick its head out through the cone. When the rat was in the holder with its head sticking out of the cone, the other end of the holder was moved forward and forced against the back of the rat so that the animal could not retract. Therefore the animal was able to move its head but not its body. This experiment was conducted using male Sprague-Dawley rats weighing 350 g (n=3, Harlan NL.) and the animals were trained for two weeks. The training sessions were designed so that the rats could get acquainted to the animal holding device and the scanning environment while remaining the head relatively still. Daily training was performed for 30 minutes for each animal.

In a second experiment, several less constrained approaches were considered. After some testing a setup with a wider tube (~ 8 cm inner diameter, length 15 cm) with transparent lids containing ventilation holes was found useful. The animal was able to groom, turn, move back and forth. The stereo camera could only be placed at the front of the PET scanner so the tube was designed so that the animal preferentially was facing towards the front. In this way the animal's head pose

could be tracked. A poking stick could be used to attract the animal's attention to face forward. An alternative method that was found to be useful was to leave the front lid open but placing the tube over a

void. The approach with the open cover could not be used in the Inveon scanner, as the scanner bore is too narrow which allows the animal to escape through the open end. This experiment was performed in female Sprague-Dawley rats weighing 250 g (n=3, Janvier FR.)

2.5.2 Awake animal scanning

Awake rat scanning was performed in the animals that were used in the second training experiment (n=2). Animals were first anesthetized (5% / 2% isoflurane mixed with medical oxygen for induction / maintenance) to attach the tracking tool and for i.v. injection of 1 mCi [^{18}F]FDG. The procedure, form start induction to end injection, takes approximately 5-10 min. Immediately after the injection, anesthesia was stopped and the animals recovered within a minute and were placed in an individual cage. After 25 minutes the animals were place in the scan tube and positioned onto the scanner. Immediately after the PET scan was started the triggering of the stereo camera and the tracking was started. A 30 minutes PET scan was acquired with the animal in awake state. After the scan the animal was anesthetized (isoflurane, cfr. supra) and positioned onto a heated animal bed in the PET scanner for an additional 30 minutes reference PET/CT scan under anesthesia. During this reference scan the small levels of head motion due to the deep breathing under anesthesia was also recorded using the stereo camera.

3. Results

3.1 Spatial calibration

The results of the spatial calibration is shown in Figure 2, where the transformed coordinate of the 22 point source in the reference frame of the stereo camera are shown along with the PET coordinates. The root mean squared error (RMSE) between the locations is 0.67 mm. The error is smallest in the center of the field of view (FOV) and gets slightly worse at the border of the FOV.

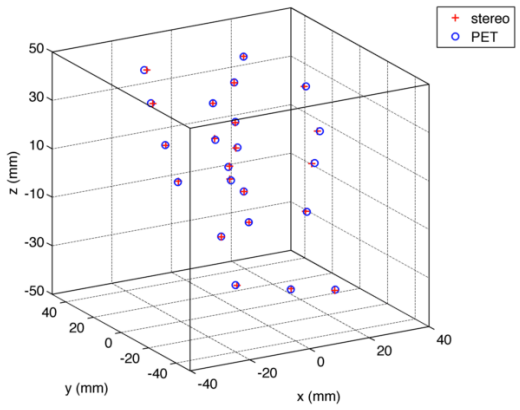

Figure 2 Spatial calibration accuracy. The positions of the point sources in the reference system of the stereo camera (red) and the transformed PET coordinates (blue).

3.2 Phantom experiments

A 3D rendering of the point source reconstructions without and with motion correction is shown in Figure 3A-B). From the reconstruction without motion correction it can be seen that there was no preferential pose during the scan, that the motion was extensive along all directions but primarily along the z direction.

The motion correction successfully recovers 7 localized point sources. To compare the motion corrected images to a static scan without any motion, profiles through the reconstructed point sources with motion correction are compared to a reconstruction of a motion free dataset in Figure 3C. It can be seen that after motion correction there is a slight blurring. The averaged FWHM of the point sources is 2.2 and 3.0 mm, in the motion free and motion corrected reconstructions.

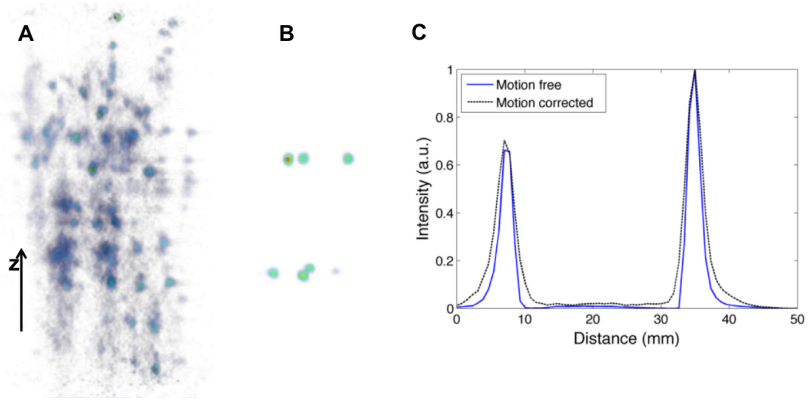

Figure 3 Results for the point source experiment. 3D rendering of reconstruction without (A) and with (B) motion correction. C) Example profiles through two point sources.

Reconstructions of the hot rod phantom without and with motion correction compared to a motion free reconstruction are shown in Figure 4.

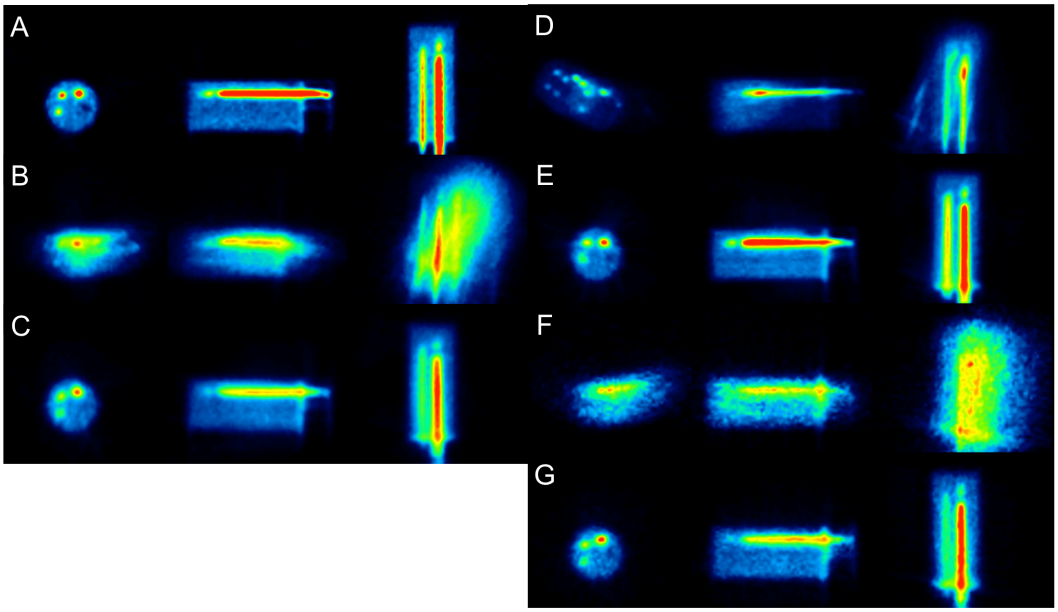

Figure 4 Results for the hot rot phantom experiment. A) reconstruction of the motion free data set (5 min scan). B)-G) pair of reconstructions without and with motion correction for the moderate motion data set (25 min scan) (B-C), the low motion (15 min scan) (D-E) and the continuous motion (5 min scan) (F-G). Inner diameters of the hot rods are 1.5, 1 and 0.8 mm.

The motion correction effectively recovers the hot rods in all cases, although some contrast is lost especially in the 0.8 mm rod. The recovery of the 2 mm cold rod can only be seen in two out of the three experiments. In general the performance of the motion correction is slightly case dependent, with the best

performance in the case of the low motion.

Reconstructions of the Derenzo resolution phantom are shown in Figure 5. Similar observations as in the hot rod phantom can be made.

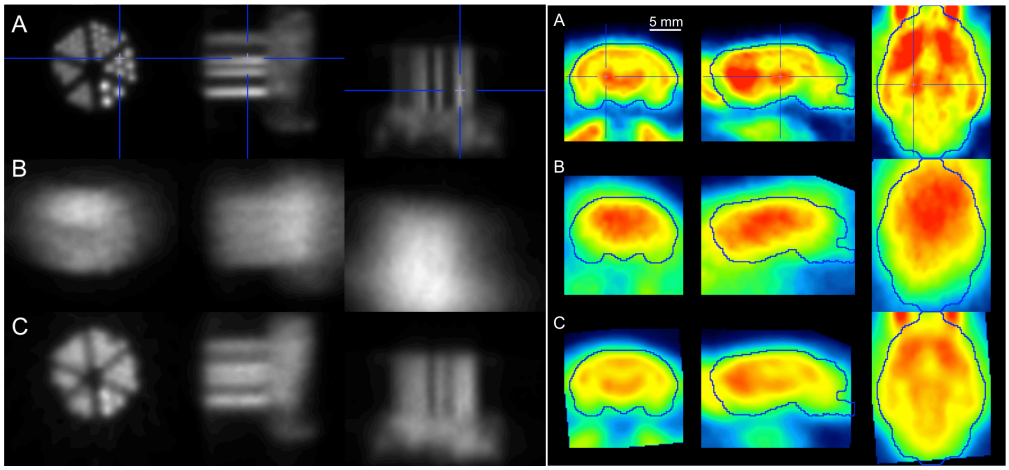

Figure 5 Results for resolution phantom (left) and the awake animal (right). A) Reference reconstruction of motion free data, B) reconstruction of a dataset with extensive movement without motion correction and C) same data as in B) but reconstruction with motion correction. The inner diameters of the hot rods are 1.5, 1.2, 1, 0.9, 0.8, 0.7 mm.

3.3 Animal experiments

Training tests with the restrained animal holder in three rats showed that the animals were experiencing a fair amount of stress. Even after two weeks of daily training sessions animals experienced some small amounts of stress. Because of the restrained nature, the stress levels and the need for labor intensive training, which could possibly also interfere with the test under study, a second experiment was performed in other animals using a wider tube. Animals were generally calm and did not show stress behavior when positioned in the tube. There seemed to be no need to train the rats but this should be further validated with new animals as the animals used in this experiment underwent several handling sessions during two weeks while we were testing several holder solutions.

Example reconstructions for one of the two animals are shown in Figure 5. The resulting motion corrected brain image recovers the general uptake pattern of the anesthetized rat data, but with some resolution loss.

4. Dissemination and valorization

The development and application of motion tracking and awake animal scanning for the Inveon PET/CT scanner is novel and consisted of several challenges compared to methods that have been developed for scanners with a wider scanner bore. Initial results are now being finalized and results have been submitted to the European Molecular Imaging Meeting (EMIM, 2014) (abstract in addendum). We are also preparing an abstract for the 2014 IEEE Medical Imaging Conference. Animal experiments, while promising, still require additional work to improve the resolution and to validate the quantification. As a result of the promising results, a Ph. D. student, Alan Miranda, was enrolled to further work on motion correction and awake animal scanning (10/2013-09/2017). With additional improvements in image quality and user friendliness, the developed animal holder, animal tracking and motion correction software can be

further valorized, to make it available to other small animal imaging centers. We are preparing applications to request appropriate development funding. Additional funding will also be sought to further extend our available expertise to motion correction for clinical brain scans.

The full list of publications and conference proceedings to which I have collaborated for the period I received funding form the BELSPO return grant (01/2012 – 12/2013) is given below.

Publications: Peer reviewed journals

1. A. J. Reader and J. Verhaeghe. "4D image reconstruction for emission tomography." *Phys. Med. Biol.* Invited review. In preparation.
2. J. Verhaeghe, T. Wyckhuys, L. wyffels, M. Schmidt, X. Langlois, S. Stroobants, and S. Staelens. "Brain normalization templates for robust VOI based analysis of small animal PET/CT imaging." *Mol. Imaging*. Submitted.
3. S. Deleye, J. Verhaeghe, L. wyffels, S. Dedeurwaerdere, S. Stroobants, and S. Staelens. "Towards a reproducible protocol for repetitive and semi-quantitative rat brain imaging with 18F-FDG: exemplified in a memantine pharmacological challenge." *Neuroimage* Submitted.
4. C. Wiebking, N. W. Duncan, P. Qin, D. J. Hayes, O. Lyttelton, P. Gravel, J. Verhaeghe, A. P. Kostikov, R. Schirrmacher, A. J. Reader, M. Bajbouj, and G. Northoff. "External awareness and GABA A multimodal imaging study combining fMRI and [18F]flumazenil-PET." *Human Brain Mapping* 35, 173–184 (2014).
5. T. Wyckhuys, J. Verhaeghe, L. wyffels, X. Langlois, M. Schmidt, S. Stroobants, and S. Staelens. "N-Acetyl-cysteine and MK-801 induced changes in glutamate levels do not affect in vivo binding of the mGluR5 radioligand [11C]ABP688 in the rat brain." *J. Nucl. Med.* 54, 1954–1961 (2013).
6. A. Fotros, K.F. Casey, K. Larcher, J. Verhaeghe, S. Cox, P. Gravel, A.J. Reader, A. Dagher, C. Benkelfat, and M. Leyton. "Cocaine Cue-Induced Dopamine Release in Amygdala and Hippocampus: A High-Resolution PET [18F]Fallypride Study in Cocaine Dependent Participants." *Neuropsychopharmacology* 38, 1780–1788 (2013).
7. J. Verhaeghe and A. J. Reader. "Accelerated PET water activation acquisition with signal separation methodology." *Med. Phys.* 40, 031909 (2013).
8. D.J. Hayes, N.W. Duncan, C. Wiebking, K. Pietruska, P. Qin, S. Lang, J. Gagnon, P. Gravel, J. Verhaeghe, A.P. Kostikov, R. Schirrmacher, A.J. Reader, J. Doyon, P. Rainville, and G. Northoff. "GABAA Receptors Predict Aversion-Related Brain Responses: An fMRI-PET Investigation in Healthy Humans." *Neuropsychopharmacology* 38, 1438–1450 (2013).
9. S. Deleye, R. Van Holen, J. Verhaeghe, S. Vandenberghe, S. Stroobants, and S. Staelens. "Performance evaluation of small-animal multipinhole mu SPECT scanners for mouse imaging." *Eur. J. Nucl. Med. Mol. Imaging* 40, 744–758 (2013).
10. P. Gravel, J. Verhaeghe, and A. J. Reader. "3D PET image reconstruction including both motion correction and registration directly into an MR or stereotaxic spatial atlas." *Phys. Med. Biol.* 58, 105–126 (2013).
11. J. Verhaeghe and A.J. Reader. "Simultaneous water activation and glucose metabolic rate imaging with PET." *Phys. Med. Biol.* 58, 393–411 (2013).
12. P. Qin, N. W. Duncan, C. Wiebking, P. Gravel, O. Lyttelton, D. J. Hayes, J. Verhaeghe, A. Kostikov, R. Schirrmacher, A. J. Reader, and G. Northoff. "GABA(A) receptors in visual and auditory cortex and neural activity changes during basic visual stimulation." *Frontiers In Human Neuroscience* 6 (2012).

Publications: Conferences

1. A. Miranda, J. Verhaghe, J. Parthoens, S. Stroobants, S. Staelens. "Motion correction for awake small animal PET imaging on the Inveon microPET". *submitted to the European Molecular Imaging Meeting, 2014*.
2. S. Deleye, J. Verhaeghe, S. Stroobants, S. Staelens. "Evaluation of the weight dependency of quantitative and semi-quantitative 18F-FDG uptake measures in rat brain" *submitted to the European Molecular Imaging Meeting, 2014*.
3. H. Amhaoul, J. Verhaeghe, J. Goossens, J. Hamaide, R. Houbrechts, L. Wyffels, J-P. Timmermans, S. Kumar-Singh, A. Katsifis, S. Staelens, S. Dedeurwaerdere. "Brain inflammation in a chronic epilepsy model:

determining the spatiotemporal profile of glial activation by in vivo 18F-PBR111 PET and standard immunohistochemistry techniques" *submitted to the European Molecular Imaging Meeting, 2014*.

4. S. Rapic, C. Vangestel, J. Verhaeghe, D. Thomae, P. Pauwels, S. De Bruyker, Y. Dockx, T. Van den Wyngaert, S. Staelesn, S. Stroobants. "Evaluation of 18F-fluorothymidine as a biomarker for early treatment response in a colorectal cancer model." *submitted to the European Molecular Imaging Meeting, 2014*.
5. H. Amhaoul, J. Verhaeghe, J. Goossens, J. Hamaide, R. Houbrechts, L. Wyffels, J-P. Timmermans, S. Kumar-Singh, S. Staelens, S. Dedeurwaerdere. "Follow-up of early brain inflammation in a rodent model of epileptogenesis with post-mortem and in vivo imaging techniques" *submitted to the Symposium on functional neuroreceptor mapping of the living brain, 2014*.
6. J. Verhaeghe, S. Deleye, H. Amhaoul, S. Stroobants, S. Dedeurwaerdere, S. Staelens. "Minimally invasive quantification of [18F]PBR111 for longitudinal in vivo imaging of brain inflammation in rat." *submitted to the Symposium on functional neuroreceptor mapping of the living brain, 2014*.
7. S. Staelens, J. Verhaeghe, T. Wyckhuys, L. Kosten, L. wyffels, S. Stroobants. "Determining mGluR5 and D2R occupancy using beta-microprobes with tracer dose as a boundary condition." *submitted to the Symposium on functional neuroreceptor mapping of the living brain, 2014*.
8. F. Elvas, S. Rapic, C. Vangestel, J. Verhaeghe, S. Staelens, S. Stroobants, C. Pak, and L. wyffels. "Influence of 99mTc-duramycin postlabelling purification on biodistribution and radiation dosimetry in mice." *submitted to 17th European Symposium on Radiopharmacy and Radiopharmaceuticals, 2014*.
9. S. Rapic, C. Vangestel, S. De Bruycker, J. Verhaeghe, Y. Dockx, L. wyffels, T. Van den Wyngaert, S. Staelen, and S. Stroobants. "Multitracer assesment of an orthotopic colorectal cancer model in mice by multimodal molecular imaging." In *Annual Meeting of the Belgian Association of Cancer Research, 2014*.
10. J. Verhaeghe, S. Deleye, H. Amhaoul, , S. Stroobants, S. Dedeurwaerdere, and S. Staelens. "Population derived and Principle Component Analysis based model for the [18F]PBR111 Arterial Input Function in Rats." In *IEEE Medical Imaging Conference* (Seoul, 2013).
11. S. Deleye, J. Verhaeghe, R. Van Holen, B. Vanderghinste, Vandenberghe S., S. Stroobants, and S. Staelens. "A whole body mouse sized muSPECT Image Quality Phantom." In *IEEE Medical Imaging Conference* (Seoul, 2013).
12. S. Rapic, S. De Bruycker, C. Vangestel, J. Verhaeghe, L. wyffels, T. Van den Wyngaert, S. Staelens, and S. Stroobants. "Multitracer Assessment of an Orthotopic Colorectal Cancer Model in Mice by Multimodel Molecular Imaging." In *VIth Anual World Molecular Imaging Congress* (Savannah, GA, USA, 2013).
13. J. Verhaeghe, T. Wyckhuys, L. wyffels, M. Schmidt, X. Langlois, S. Stroobants, and S. Staelen. "Robust VOI based analysis of mGluR5 imaging in rat brain using [11C]ABP688." In *XIth International Conference on Quantification of Brain Function With PET* (China, 2013).
14. M. Milella, M.S. Minuzzi, M. Leyton, C. Benkelfat, J.-P. Soucy, Kirlow A., Schirrmacher E., Angle M., J. Verhaeghe, G. Massarweh, A.J. Reader, A. Alliaga, J.E. Peixoto Santos, M.-C. Guiot, E. Kobayashi, and P. Rosa-Neto. "Quantification Of [11C]ABP688 Binding In The Human Brain Using Cerebellum As Reference Region: Interpretation And Limitations." In *XIth International Conference on Quantification of Brain Function With PET* (Shanghai, China, 2013).
15. T. Wyckhuys, J. Verhaeghe, L. wyffels, M. Schmidt, X. Langlois, S. Stroobants, and S. Staelen. "Pharmacological induced changes in glutamate levels do not affect mGluR5 radioligand [11C]ABP688 binding in the brain." In *XIth International Conference on Quantification of Brain Function With PET* (Shanghai, China, 2013).
16. T. Wyckhuys, J. Verhaeghe, L. wyffels, M. Schmidt, X. Langlois, S. Stroobants, and S. Staelen. "Comparison between beta-microprobe and microPET in investigating receptor binding exemplified by the mGluR5 tracer [11C]ABP688." In *XIth International Conference on Quantification of Brain Function With PET* (Shanghai, China, 2013).
17. S. Deleye, J. Verhaeghe, T. Wyckhuys, L. wyffels, S. Dedeurwaerdere, S. Stroobants, and S. Staelens. "Correcting for accurately measured glucose levels improves the robustness of PET rat brain image quantification in longitudinal experiments." In *XIth International Conference on Quantification of Brain Function With PET* (Shanghai, China, 2013).
18. L. wyffels, A-M. Waldron, J. Verhaeghe, D. Vanderghinste, X. Langlois, M. Schmidt, S. Stroobants, and S. Stae- lens. "Optimization of the automated synthesis of [18F]AV45 on a Veenstra FluorSynthon I module for microPET imaging in a transgenic mouse model of Alzheimer's disease." *International Symposium for*

Radiopharmaceutical Sciences (Jeju, Korea, 2013).

19. A-M. Waldron, J. Verhaeghe, L. wyffels, C. Bigot, M. Schmidt, X. Langlois, Van Der Linden A., S. Stroobants, and S. Staelens. "Mice strain differences in small animal PET [11C]-PiB and [18F]-Florbetaben imaging of beta- amyloid plaques." In *Annual Meeting of the Society of Nuclear Medicine and Molecular Imaging* (Vancouver,BC, Canada, 2013).
20. H. Amhaoul, J. Goosens, J. Hamaide, K. Szewczyk, A. Van Eetveldt, K. Van den Eynde, I. Pintelon, wyffels L., J. Verhaeghe, Kumar-Singh S., S. Staelen, and S. Dedeurwaerdere. "Characterization of brain inflammation in a chronic epilepsy model by means of post-mortem and in vivo techniques." In *Belgian Molecular Imaging Congres* (Leuven, Belgium, 2013).
21. A-M. Waldron, J. Verhaeghe, wyffels L., C. Bigot, X. Langlois, M. Schmidt, A. Van der Linden, S. Stroobants, and S. Staelens. "Small animal PET for the non-invasive detection of beta-amyloid plaques; an evaluation of transgenic models with [11C]-PiB and [18F]-Florbetaben." In *Belgian Molecular Imaging Congress* (Leuven, Belgium, 2013).
22. T. Wyckhuys, J. Verhaeghe, wyffels L., M. Schmidt, X. Langlois, S. Stroobants, and S. Staelens. "Com- paring beta-microprobe and microPET in investigating receptor binding exemplified by the mGluR5 tracer [11C]ABP688." In *Belgian Molecular Imaging Congress* (Leuven, Belgium, 2013).
23. L. Wyffels, T. Wyckhuys, J. Verhaeghe, M. Schmidt, X. Langlois, S. Stroobants, and S. Staelens. "N-Acetyl-cysteine and MK-801 induced changes in glutamate levels do not affect mGluR5 radioligand [11C]ABP688 binding in the rat brain." In *Belgian Molecular Imaging Congress* (Leuven, Belgium, 2013).
24. J. Verhaeghe, T. Wyckhuys, wyffels L., M. Schmidt, X. Langlois, S. Stroobants, and S. Staelens. "[11C]ABP688 brain templates for robust VOI based analysis of mGluR5 imaging in rat brain." In *Belgian Molecular Imaging Congress* (Leuven, Belgium, 2013).
25. L. Kosten, T. Wyckhuys, J. Verhaeghe, L. wyffels, L. De Picker, S. Dedeurwaerdere, S. Stroobants, and S. Staelens. "Longitudinal evaluation of the glutamatergic pahtway in a schizophrenia rat model of chronic NMDA hypofunction." In *VIth Anual World Molecular Imaging Congress* (Savannah, GA, USA, 2013).
26. J. Parthoens, V. Engelen, T. Wyckhuys, J. Verhaeghe, S. Stroobants, and S. Staelens. "Dopaminergic modulation in rats by Deep Brain Stimulation of the medial prefrontal cortex: quantification of [11C]-raclopride D2R binding in the caudate putamen using microPET." In *VIth Anual World Molecular Imaging Congress* (Savannah, GA, USA, 2013).
27. A-M. Waldron, Kelley J.B., L. wyffels, J. Verhaeghe, Richardson J.C., S. Dedeurwaerdere, S. Stroobants, X. Lan- glois, and S. Staelens. "In vivo PET imaging of amyloid pathology and brain metabolism in a double transgenic model of Alzheimer's disease." In *VIth Anual World Molecular Imaging Congress* (Savannah, GA, USA, 2013).
28. P. Gravel, J. Verhaeghe, and A.J. Reader. "Direct 4D PET Reconstruction of Parametric Images into a Stereotaxi Brain Atlas for [11C]Raclopride." In *Proceedings of the 2012 IEEE Medical Imaging Conference* (Seoul, South Korea, 2012).
29. S. Hafezian, J. Cottitto, A.J. Reader, and J. Verhaeghe. "Metric for fast automated relative assessment of motion correction methods for dynamic PET imaging." In *Proceedings of the 2012 IEEE Medical Imaging Conference* (Anaheim, CA, USA, 2012).
30. E. Letrourneau, J. Verhaeghe, and A. Reader. "Impact of tracer distribution, count level, iterations and post-smoothing on PET quantification using a variously weighted least squares algorithm." In *Proceedings of the 2012 IEEE Medical Imaging Conference* (2012).S. Deleye, D. Smits, L. wyffels, J. Verhaeghe, T. Wyckhuys, X. Langlois, M. Schmidt, S. Dedeurwaerdere, S. Stroobants, and S. Staelens. "Protocol optimization to further reduce intra- and inter-animal variability in microPET rat brain image quantification." In *annual meeting of the European Association of Nuclear Medicine* (2012).
31. A. Fotros, K.F. Casey, K. Larcher, J. Verhaeghe, S. Cox, P. Gravel, A.J. Reader, A. Dagher, C. Benkelfat, and M. Leyton. "Drug Cue-Induced Dopamine Release in Amygdala and Hippocampus: A High-Resolution PET [18F]Fallypride Study in Cocaine Dependent Participants." *Annual Meeting of the American College of Neuropsychopharmacology*, ,2012.
32. A. Fotros, K.F. Casey, K. Larcher, J. Verhaeghe, S. Cox, P. Gravel, A.J. Reader, A. Dagher, C. Benkelfat, and M. Leyton. "Cue-induced dopamine release in striatal and extra-striatal regions in cocaine dependent users: a high-resolution PET [18F]fallypride study." In The *10th International Catecholamine Symposium* (Pacific

Grove, CA, 2012).

33. A. Fotros, K.F. Casey, K. Larcher, J. Verhaeghe, S. Cox, P. Gravel, A.J. Reader, A. Dagher, C. Benkelfat, and M. Leyton. "Cue-induced dopamine release in striatal and extra-striatal regions in cocaine dependent users: a high-resolution PET [18F]fallypride study." In *Canadian College of Neuropsychopharmacology* (Vancouver, BC, 2012).
34. A. Fotros, K.F. Casey, K. Larcher, J. Verhaeghe, S. Cox, P. Gravel, A.J. Reader, A. Dagher, C. Benkelfat, and M. Leyton. "Cue-induced dopamine release in striatal and extra-striatal regions in cocaine dependent users: a high-resolution PET [18F]fallypride study." In *Society for Biological Psychiatry*, 71, p. 272S (Philadelphia, PA, 2012).
35. P. Qin, S. Grimm, N. Duncan, C. Wiebking, O. Lyttelton, D. Hayes, P. Gravel, J. Verhaeghe, A. Kostikov, R. Schirrmacher, et al. "GABA-A receptors and the transition from resting-state to stimulus induced activity." In *Human Brain Mapping* (Beijing, China, 2012).

Conference attendance

I have attended the following conferences: Belgian Molecular Imaging Congress (21/03/2013, Leuven, Belgium), XIth International Conference on Quantification of Brain Function with PET (Shanghai, China, 20/05 – 23/05, 2013), the IEEE Medical Imaging Conference (Seoul, Korea, 27/10 – 2/11 2013). I had also planned to attend the 2012 IEEE Medical Imaging Conference but due to air traffic disruptions (storm Sandy) I was unable to attend.

The IEEE conferences are highly relevant as the engineering and application aspects of motion correction (head motion, respiratory motion, animal motion, ...) is a well covered topic during the conference. The other conferences are part of my further integration into the host institution research group (MICA) covering broader molecular imaging topics. At these conferences I have presented work that resulted from my integration and collaboration in the lab concerning improved quantification in brain PET.

5. Evaluation and Outlook

Overall the integration into the research group can be evaluated as very positive. Whilst the motion correction and awake scanning project is not yet at the final application stage very promising progress has been made. The research group and myself are confident that further research and development can bring the current approach to the final application stage. Therefore, a PhD student was hired to further advance the awake scanning project under my supervision.

I have also been able to make significant contribution to multiple interesting research projects at MICA, which has resulted in a number of publications (see above for a detailed list). Furthermore I have secured additional funding for research at MICA on various important topics for the lab: Dual tracer PET imaging (FWO, research grant), Quantification of FDG brain PET imaging in rat (BOF, small fundamental research project), tumor uptake quantification (iMinds, ICON). In addition to the PhD student working on motion correction and awake animal scanning, I also supervise a PhD student working on quantification in longitudinal and static molecular imaging of small animals.

After the BELSPO funding I have been employed by the MICA research group (internal funding) as a postdoctoral researcher for an indefinite period. In the future I hope to further make significant contributions for MICA and eventually progress to the level of reader.