Objective B: Hidex AMG

The full characterization of the Hidex AMG (Hidex, Finland) included the investigation into the effect of varying sample volume and defining the optimal range of sensitivity of the instrument. This was achieved by conducting multiple experiments using both 18F and 11C as gamma-emitting sources. Prior to each experiment, a quality control, and eventually a re-calibration was performed, using a 137Csactivity source (Hidex, Finland, 137Cs Quality Control-3.36 kBq, *t*1/2 = 11,018.3 days, Eγ = 550-750 keV) to get a peak position in the channel corresponding to 662 ±10 keV, a resolution of 10±5% and an efficiency of 18±5% within a 550-750 keV energy window. The stability of the QC measurement was assessed when the crystal of the AMG was allowed to warm up for four hours versus no warm-up time. All 18F samples were counted for 60 seconds unless otherwise stated, using an energy window of 400-600 keV around the 511-keV coincidence peak for 18F.

Each counting acquisition will provide a series of values for individual samples, including counted time, dead time factor, raw counts, counts per minute (CPM). The Hidex AMG interface automatically calculates several outputs. Raw counts are calculated from the spectrum to the 400-600 keV template window using the formula,

Equation 7

The automatic dead time factor (DTF) implemented is determined by the dead time of the instrument and actual activity using the formula,

Equation 8

The count and dead time factor are used to calculate the counts per minute (CPM) for each measurement using the formula,

Equation 9

The AMG will automatically decay-correct CPM to calculate normalized CPM values. This normalized activity is calculated to a time of reference (*t0*) usually representing the time and activity of the first sample in the acquisition based on the half-life of radioisotope,using the formula,

Equation 10

Where, A0 is the normalized CPM, A is the measured CPM, T1/2 is the isotope half-life (109.8 min for 18F, and 20.38 min for 11C) [69], and t is the time respect to t0. The counting efficiency was calculated based on the normalized CPM values and known activity of the sources, using the formula,

Equation 11

For the presentation of the results the activities were expressed in nanocurie (nCi).

Experiment 1: Background Correction

The influence of background noise and the effectiveness of the Hidex AMG shielding system was assessed by the repeated measurement of the activity detected from an empty (nonradioactive) sample, positioned next to adjacent radioactive samples in the 13-mm rack. All samples collected were corrected for background noise by subtracting the activity (in Bq) detected from a blank tube from the total activity of each sample. The blank tube was positioned so that it was always the first measurement of each rack counted in the data acquisition and contained no radioactivity, with all proceeding hot samples placed and counted adjacent to the blank measurement. There were no observed significant patterns of change of the background activity counts therefore, the activity across all blank measurements was averaged and used as a single value that was subtracted from the total sample activity to obtain the final background corrected value.

Experiment 2: Efficiency of Response

The efficiency of each gamma counting instrument can be highly variable and is dependent on the species of isotope being measured. An experimental measure of counting efficiency by the Hidex AMG was assessed with the goal of cross-calibrate it with the other devices in the institution for the isotope of interest (11C and 18F).

The cross-calibration between a Capintec™ Dose Calibrator and the AMG was performed to determine the efficiency of the AMG respect to the values read in the Capintec™ Dose Calibrator using a 18F source. The experiment began with the preparation of a 200 mL aqueous solution of 12,000 nCi of 18F. This solution was then used to prepare a total of eight samples of different geometry and volume. Samples included four 3.0 mL aliquots in 4 mL ETDA tubes and four 1.0 mL aliquots in 3 mL polystyrene tubes. Again, the first measurement was reserved for the background count with no activity. Data acquisition was recorded over the course of 35 hrs (n=88 paired measurements), with a counting time of 60 seconds and a decay correction to the time of the initial activity measurement by the synchronized dose calibrator.

To assess the linearity of the response of the Hidex AMG respect of the activity of the sample, the decay per minute (DPM) of the sample given by the dose calibrator was calculated using the half-life of the radioactive decay. The activity measured by the AMG was background corrected and converted from Becquerels (Bq) to nCi. The percent efficiency was calculated using the formula, [70]

Equation 12

The average efficiency for both the EDTA and polystyrene tube were determined to evaluate the optimal range of activity with respect to 18F.

Experiment 3: Sample Volume and Geometry

The effect of sample volume on the count rate and relative efficiency of the AMG was assessed using an experiment to analyze samples of 18Fwith a constant activity and varying volumes. This effect can be attributed to the loss emitted photons that have a greater likelihood of escaping through the hole of the detector well when volume increases (depicted in Figure 2) [12]. The efficiencies for several types of tubes with varying volumes were determined.

a. Validation of Effect.

The experimental design involved the preparation of a 1000 nCi sample of 18Fin 1.0 mL aqueous solution. The initial time and activity at production was recorded, and 0.1 mL aliquots of this stock solution was then placed into two 4 mL (13-mm x 75-mm) EDTA blood tubes to make samples an approximate activity of 100 nCi. One additional vial was reserved for the background measurement with no activity. An initial count of 150s was acquired for both samples as a reference count rate with low noise. An additional forty 60 sec count measurements were performed, adding a 100 µL aliquot of non-radioactive water to the vials between each measurement. The volume of the sample was gradually increased between each measurement between 0.1 and 4.0 mL, while maintaining the total activity. This data was used to estimate the percent counting efficiency of 18Fwith respect to varying sample volume.

b. Effect of Volume on Radiometabolite Experiments

These experiments assessed the counting efficiencies of the varying sample volumes and tubes used during plasma radiometabolite analysis. To begin, a radioactive sample of 18F was acquired with a starting activity of 2.24x106 nCi in 4.0 mL of aqueous solution. This initial sample was diluted deionized water and mixed thoroughly to create a desired solution with a concentration of approximately 500 nCi/mL. To determine the individual efficiencies of all the possible volumes for the Oasis filter eluents during radiometabolite analysis, eight 4 mL (13-mm x 75-mm) EDTA blood tubes were used with volumes ranging from 0.5 – 4.0 mL, increasing by 0.5 mL between each sample. These samples were measured at five time points to acquire matched duplicate values of efficiency. A similar design was used for the 5 mL polystyrene tubes used to hold the whole blood/plasma aliquots during metabolite analysis. For this step, 0.3 mL radioactive sample was aliquoted into one tube, and a second 0.6 mL sample was aliquoted into a separate tube. Again, these were measured five times to acquire duplicate results to calculate averaged efficiency values between each sample volume.

Objective B: Characterization of the response of the Hidex AMG

E1. Background correction

The experiments did not show any systematic pattern of the background counts, including low and constant measurements. Therefore, the background counts across all measurements within a specified acquisition were averaged and subtracted from the counts for the radioactive samples before decay correction. The results confirmed that there is low penetration of the lead-shielding for the environmental radiation.

E2. Optimal Range of Activity plot

The results displayed in Figure 3 provide information on the capacity of the NaI crystal detector of the AMG for capturing large volume of positron annihilation events. It is observed in Figure 4 that at high concentrations of activity, the dead time of the detector increases, and therefore decreasing the precent counting efficiency. On the other hand, at low concentrations of activity, the average counting efficiencies show high levels of variability.

**Figure 4.** The percent efficiency/branching ratio for 18F, accounting for the radioactive decay of the isotope, as a function of the logarithmic scale of the average activity between the 3 mL and 1 mL samples. Data was acquired in the window centered around the coincidence sum peak (400-600 keV).

From these results, it was determined that the optimal range of activity for the capacity of the AMG detector was observed between 10-500 nCi. The average percent efficiency (mean±SD) corrected for the branching ratio of 18F (0.967) for both the 3 mL and 1 mL samples within the optimal range of sensitivity (10-500 nCi) were determined to be 37.5±0.2% and 39.1±0.4% respectively (Figure 5). Experiment 3 expands on the effect of volume on counting efficiency.

**Figure 5.** The average percent efficiency/branching ratio for 18F the 3 mL (green) and 1 mL (blue) samples within the optimal range of 10-500 nCi, accounting for the radioactive decay of the isotope. Vials 1-4 consisted of 3mL aliquots in 4mL EDTA blood tubes; Vials 5-8 consisted of 1 mL aliquots in 3 mL polystyrene tubes. Data was acquired in the window centered around the coincidence sum peak (400-600 keV).

E3. Sample Volume Effect on Relative Efficiency

The average percent efficiency (mean±SD) of the initial 150-s reference measurement between the two samples was determined to be 36.7±0.3% which was used to compare the efficiencies of the following forty measurements. Figure 6 represents the absolute efficiency as a function of increasing sample volume acquired in the window centered around the 511 keV energy window for 18F(400-600 keV). It was observed that there is an increasing likelihood of the escape of photons from the top of the well as sample volume increases, subsequently decreasing the count efficiency for those samples. It is observed in Figure 6 that between 0.1 – 2.0 mL the percent efficiency for both samples of 18F are in close agreeance with the reference measurement with low levels of noise. The average percent efficiency for the two samples were found to be 35.4±1% and 36.2±1% respectively. Volumes above 2.0 mL begin to have greater dispersion and begin to a decrease in percent efficiency. This observation provides evidence that the optimal range for sample volume is between 0.1 and 2.0 mL for 18F.

**Figure 6.** Percent efficiency of the AMG for 18 F as a function of sample volume. Two samples of 100 nCi in 4 mL EDTA tubes were measured in the 13 mm x 75 m Hidex racks. Data was acquired in the window centered around 18F511 keV energy window.

Figure 7 shows the difference in efficiency of the Hidex AMG for 11C in a range of sample volumes from 0.3 – 4.0 mL, representing the various sample sizes required for plasma metabolite analysis during [11C]CURB PET imaging. The average efficiency using a window of energy between 400-600 keV was 32.7%. When using an energy window that is centered exactly ±20% of the 511 keV coincidence peak (409-613 keV), the efficiency stayed relatively stable with an average efficiency of 33.0%.

**Figure 7.** Percent efficiency of the AMG for 11C as a function of increasing sample volume acquired during plasma metabolite analyses.

Summary

Due to the necessity of additional instruments for obtaining the arterial plasma and radiometabolite activity measurements, there will always be a level of variability and uncertainty introduced to the data across measuring instruments. Through the characterization and rigorous calibration of all gamma counting instruments, including the ABSS and AMG, the uncertainty and error introduced to the data collected can be minimized. The characterization of both the ABSS and AMG instruments used for arterial blood sampling showed that the response of both gamma counters are stable and reproducible with minimal uncertainty.

.

Characterization of Instruments used for Arterial Sampling

The second sub-objective of Aim I characterized the response of the Hidex AMG, and the average efficiency and optimal range of activity were determined. Figure 4 (Section 3.2.2.2) depicts the average percent efficiency in both the 3.0 mL and 1.0 mL samples as a function of the logarithmic scale of activity (nCi), which indicated that the optimal range of activity of the AMG detector exists between 10-500 nCi. The results here provide information on the capacity of the AMG system for counting larger number of positron emission events, where at high concentrations of radioactivity the detector deadtime increases and therefore decreasing the overall counting efficiency.

From Figure 4, the average counting efficiency of 18F for the 1.0 mL and 3.0 mL within the proposed optimal range of sensitivity of 10-500 nCi (Figure 5, Section 3.2.2.2) were determined to be 39.1±0.4% and 37.5±0.2% respectively. The results from the final experiment characterized the effect of sample volume on the average counting efficiency of measurements. As depicted in Figure 6 (Section 3.2.2.3) there is an observable decrease in the relative counting efficiency of the AMG with increasing sample volume. This can be explained by the effect of the loss captured counted of emitted photons due to the geometry of positron emission (Figure 2, Section 2.6.3), resulting in more counts detected in the 511 keV peak ROI since there is less likelihood of capturing both photons in coincidence in the 1022 keV peak ROI. These results are consistent with the results of a similar study that characterized a commercial well-type NaI(TI) gamma counter for PET applications (Wizard2, PerkinElmer, Waltham, MA, USA) [77]. Here, Martin A. Lodge *et al.* (2015) reported a similar effect, where the relative efficiencies centered around the 511-keV photon peak were less susceptible to changes in sample volumes than those of single-photon emitters.

A similar experiment was conducted, instead to determine the average counting efficiency of 11C as a function of increasing sample sizes that represent the volumes required for plasma metabolite analysis of [11C]CURB. Again, there is an observed decrease in the counting efficiency of 11C as sample volumes increase. In addition, the average percent efficiency of data measured within the counting window of energy used in the SOP for the metabolite analyses (400-600 keV) was compared to that of the average percent efficiency of data acquired in an energy window that is centered exactly ±20% of the 511 keV peak (409-613 keV). The efficiency for the 400-600 keV energy window and the 409-613 keV energy window were determined to be 32.7% and 33.0% respectively, which validates the accuracy of the window of energy used for the plasma metabolite analyses. The observation that the percent efficiency for 11C is lower than that of 18F is surprising since all data was corrected for the branching ratio of each radioisotope. Some possible explanations include the potential higher levels of adhesion of 11C to the syringes used to transfer the solutions and any other elements used when diluting the solutions. In addition, the short half-life of 11C makes it particularly more challenging to account for measurement error corrections.

1. References

[1] Garani R, Watts JJ, Mizrahi R. Endocannabinoid system in psychotic and mood disorders, a review of human studies. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021;106:110096. doi:10.1016/j.pnpbp.2020.110096

[2] Rusjan PM, Wilson AA, Mizrahi R, Boileau I, Chavez SE, Lobaugh NJ, Kish SJ, Houle S, Tong J. Mapping Human Brain Fatty Acid Amide Hydrolase Activity with PET. Journal of Cerebral Blood Flow & Metabolism. 2013;33(3):407–414. doi:10.1038/jcbfm.2012.180

[3] Carson RE. 6 Tracer Kinetic Modeling in PET. Positron Emission Tomography: Basic Science and Clinical Practice. 2003:147–179.

[4] Ghosh KK, Padmanabhan P, Yang C-T, Mishra S, Halldin C, Gulyás B. Dealing with PET radiometabolites. EJNMMI Research. 2020;10:109. doi:10.1186/s13550-020-00692-4

[5] Tonietto M, Rizzo G, Veronese M, Fujita M, Zoghbi SS, Zanotti-Fregonara P, Bertoldo A. Plasma radiometabolite correction in dynamic PET studies: Insights on the available modeling approaches. Journal of Cerebral Blood Flow & Metabolism. 2016;36(2):326–339. doi:10.1177/0271678X15610585

[6] Jons PH, Ernst M, Hankerson J, Hardy K, Zametkin AJ. Follow-up of radial arterial catheterization for positron emission tomography studies. Human Brain Mapping. 1997;5(2):119–123. doi:10.1002/(SICI)1097-0193(1997)5:2<119::AID-HBM5>3.0.CO;2-6

[7] Gunn R. Mathematical Modelling and Identifiability Applied to Positron Emission Tomography Data. 1996:227.

[8] Nakao R, Schou M, Halldin C. Rapid metabolite analysis of positron emission tomography radioligands by direct plasma injection combining micellar cleanup with high submicellar liquid chromatography with radiometric detection. Journal of Chromatography A. 2012;1266:76–83. doi:10.1016/j.chroma.2012.10.022

[9] Katsifis A, Loc’h C, Henderson D, Bourdier T, Pham T, Greguric I, Lam P, Callaghan P, Mattner F, Eberl S, et al. A rapid solid-phase extraction method for measurement of non-metabolised peripheral benzodiazepine receptor ligands, [(18)F]PBR102 and [(18)F]PBR111, in rat and primate plasma. Nuclear Medicine and Biology. 2011;38(1):137–148. doi:10.1016/j.nucmedbio.2010.07.008

[10] Boellaard R, van Lingen A, van Balen SCM, Hoving BG, Lammertsma AA. Characteristics of a new fully programmable blood sampling device for monitoring blood radioactivity during PET. European Journal of Nuclear Medicine. 2001;28(1):81–89. doi:10.1007/s002590000405

[11] Programmable Blood Sampler (PBS-101-UM-01-EN): Use and maintenance manual. 2014.

[12] Lodge MA, Holt DP, Kinahan PE, Wong DF, Wahl RL. Performance assessment of a NaI(Tl) gamma counter for PET applications with methods for improved quantitative accuracy and greater standardization. EJNMMI Physics. 2015;2:11. doi:10.1186/s40658-015-0114-3

[13] Haaf FELT, Verheijke ML. An improved gamma well counter for radioactive tracer applications. The International Journal of Applied Radiation and Isotopes. 1976;27(2):79–84. doi:10.1016/0020-708X(76)90180-0

[14] Gunn RN, Gunn SR, Cunningham VJ. Positron Emission Tomography Compartmental Models. Journal of Cerebral Blood Flow & Metabolism. 2001;21(6):635–652. doi:10.1097/00004647-200106000-00002

[15] Daghighian F, Sumida R, Phelps ME. PET Imaging: An Overview and Instrumentation. Journal of Nuclear Medicine Technology. 1990;18(1):5–13.

[16] Townsend D. Physical Principles and Technology of Clinical PET Imaging. 2004;33(2).

[17] Zhu Y, Zhu X. MRI-Driven PET Image Optimization for Neurological Applications. Frontiers in Neuroscience. 2019;13:782. doi:10.3389/fnins.2019.00782

[18] Chen Y, An H. Attenuation Correction of PET/MR Imaging. Magnetic resonance imaging clinics of North America. 2017;25(2):245–255. doi:10.1016/j.mric.2016.12.001

[19] Rusjan P, Mamo D, Ginovart N, Hussey D, Vitcu I, Yasuno F, Tetsuya S, Houle S, Kapur S. An automated method for the extraction of regional data from PET images. Psychiatry Research: Neuroimaging. 2006;147(1):79–89. doi:10.1016/j.pscychresns.2006.01.011

[20] Gunn RN, Gunn SR, Cunningham VJ. Positron Emission Tomography Compartmental Models. Journal of Cerebral Blood Flow & Metabolism. 2001;21(6):635–652. doi:10.1097/00004647-200106000-00002

[21] Morris ED, Endres CJ, Schmidt KC, Christian BT, Jr RFM, Fisher RE. Kinetic Modeling in Positron Emission Tomography.

[22] Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang S-C, Ichise M, et al. Consensus Nomenclature for in vivo Imaging of Reversibly Binding Radioligands. Journal of Cerebral Blood Flow & Metabolism. 2007;27(9):1533–1539. doi:10.1038/sj.jcbfm.9600493

[23] Wilson AA, Garcia A, Parkes J, Houle S, Tong J, Vasdev N. [11C]CURB: Evaluation of a novel radiotracer for imaging fatty acid amide hydrolase by positron emission tomography. Nuclear Medicine and Biology. 2011;38(2):247–253. doi:10.1016/j.nucmedbio.2010.08.001

[24] Rusjan PM, Wilson AA, Mizrahi R, Boileau I, Chavez SE, Lobaugh NJ, Kish SJ, Houle S, Tong J. Mapping Human Brain Fatty Acid Amide Hydrolase Activity with PET. Journal of Cerebral Blood Flow & Metabolism. 2013;33(3):407–414. doi:10.1038/jcbfm.2012.180

[25] Palermo G, Branduardi D, Masetti M, Lodola A, Mor M, Piomelli D, Cavalli A, De Vivo M. Covalent inhibitors of fatty acid amide hydrolase (FAAH): A rationale for the activity of piperidine and piperazine aryl ureas. Journal of medicinal chemistry. 2011;54(19):6612–6623. doi:10.1021/jm2004283

[26] Ahn K, McKinney MK, Cravatt BF. Enzymatic Pathways That Regulate Endocannabinoid Signaling in the Nervous System. Chemical Reviews. 2008;108(5):1687–1707. doi:10.1021/cr0782067

[27] Skaper SD, Di Marzo V. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Philosophical Transactions of the Royal Society B: Biological Sciences. 2012;367(1607):3193–3200. doi:10.1098/rstb.2012.0313

[28] Pertwee RG, Howlett AC, Abood ME, Alexander SPH, Di Marzo V, Elphick MR, Greasley PJ, Hansen HS, Kunos G, Mackie K, et al. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB 1 and CB 2. Pharmacological Reviews. 2010;62(4):588–631. doi:10.1124/pr.110.003004

[29] Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, Piomelli D, Davison JS, et al. Identification and Functional Characterization of Brainstem Cannabinoid CB2 Receptors. Science. 2005;310(5746):329–332. doi:10.1126/science.1115740

[30] Pertwee RG, Ross RA. Cannabinoid receptors and their ligands. Prostaglandins, Leukotrienes and Essential Fatty Acids (PLEFA). 2002;66(2–3):101–121. doi:10.1054/plef.2001.0341

[31] McKinney MK, Cravatt BF. Structure and Function of Fatty Acid Amide Hydrolase. Annual Review of Biochemistry. 2005;74(1):411–432. doi:10.1146/annurev.biochem.74.082803.133450

[32] Activation of the endocannabinoid system by organophosphorus nerve agents - PMC. [accessed 2023 Feb 10]. https://www-ncbi-nlm-nih-gov.proxy3.library.mcgill.ca/pmc/articles/PMC2597283/

[33] Hillard CJ. The Endocannabinoid Signaling System in the CNS. In: International Review of Neurobiology. Vol. 125. Elsevier; 2015. p. 1–47. https://linkinghub.elsevier.com/retrieve/pii/S0074774215001324. doi:10.1016/bs.irn.2015.10.001

[34] Jacobson MR, Watts JJ, Da Silva T, Tyndale RF, Rusjan PM, Houle S, Wilson AA, Ross RA, Boileau I, Mizrahi R. Fatty Acid Amide Hydrolase is Lower in Young Cannabis Users. Addiction biology. 2021;26(1):e12872. doi:10.1111/adb.12872

[35] Watts JJ, Jacobson MR, Lalang N, Boileau I, Tyndale RF, Kiang M, Ross RA, Houle S, Wilson AA, Rusjan P, et al. Imaging brain fatty acid amide hydrolase in untreated patients with psychosis. Biological psychiatry. 2020;88(9):727–735. doi:10.1016/j.biopsych.2020.03.003

[36] Lorthois S, Duru P, Billanou I, Quintard M, Celsis P. Kinetic modeling in the context of cerebral blood flow quantification by H2(15)O positron emission tomography: the meaning of the permeability coefficient in Renkin-Crone׳s model revisited at capillary scale. Journal of Theoretical Biology. 2014;353:157–169. doi:10.1016/j.jtbi.2014.03.004

[37] Arakawa R, Takano A, Nag S, Jia Z, Amini N, Maresca KP, Zhang L, Keliher EJ, Butler CR, Piro JR, et al. Target occupancy study and whole-body dosimetry with a MAGL PET ligand [11C]PF-06809247 in non-human primates. EJNMMI Research. 2022;12(1):13. doi:10.1186/s13550-022-00882-2

[38] Boileau I, Rusjan PM, Williams B, Mansouri E, Mizrahi R, Luca VD, Johnson DS, Wilson AA, Houle S, Kish SJ, et al. Blocking of Fatty Acid Amide Hydrolase Activity with PF-04457845 in Human Brain: A Positron Emission Tomography Study with the Novel Radioligand [11C]CURB. Journal of Cerebral Blood Flow & Metabolism. 2015;35(11):1827–1835. doi:10.1038/jcbfm.2015.133

[39] Logan J, Fowler JS, Volkow ND, Wang G-J, MacGregor RR, Shea C. Reproducibility of repeated measures of deuterium substituted [11C]L-deprenyl ([11C]L-deprenyl-D2) binding in the human brain. Nuclear Medicine and Biology. 2000;27(1):43–49. doi:10.1016/S0969-8051(99)00088-8

[40] Pike VW. PET Radiotracers: crossing the blood-brain barrier and surviving metabolism. Trends in pharmacological sciences. 2009;30(8):431. doi:10.1016/j.tips.2009.05.005

[41] Aarnio R, Alzghool OM, Wahlroos S, O’Brien-Brown J, Kassiou M, Solin O, Rinne JO, Forsback S, Haaparanta-Solin M. Novel plasma protein binding analysis method for a PET tracer and its radiometabolites: A case study with [11C]SMW139 to explain the high uptake of radiometabolites in mouse brain. Journal of Pharmaceutical and Biomedical Analysis. 2022;219:114860. doi:10.1016/j.jpba.2022.114860

[42] Bentourkia M. Determination of the Input Function at the Entry of the Tissue of Interest and Its Impact on PET Kinetic Modeling Parameters. Molecular Imaging and Biology. 2015;17(6):748–756. doi:10.1007/s11307-015-0895-8

[43] Graham MM, Lewellen BL. High-Speed Automated Discrete Blood Sampling for Positron Emission Tomography.

[44] van der Weijden CWJ, Mossel P, Bartels AL, Dierckx RAJO, Luurtsema G, Lammertsma AA, Willemsen ATM, de Vries EFJ. Non-invasive kinetic modelling approaches for quantitative analysis of brain PET studies. European Journal of Nuclear Medicine and Molecular Imaging. 2023;50(6):1636–1650. doi:10.1007/s00259-022-06057-4

[45] Gumbleton M, Oie S, Verotta D. Pharmacokinetic-pharmacodynamic (PK-PD) modelling in non-steady-state studies and arterio-venous drug concentration differences. British Journal of Clinical Pharmacology. 1994;38(5):389–400. doi:10.1111/j.1365-2125.1994.tb04372.x

[46] Tomasi G, Veronese M, Bertoldo A, Smith CB, Schmidt KC. Substitution of venous for arterial blood sampling in the determination of regional rates of cerebral protein synthesis with L-[1-11C]leucine PET: A validation study. Journal of Cerebral Blood Flow & Metabolism. 2019;39(9):1849–1863. doi:10.1177/0271678X18771242

[47] Green JH, Ellis FR, Shallcross TM, Bramley PN. Invalidity of hand heating as a method to arterialize venous blood. Clinical Chemistry. 1990;36(5):719–722.

[48] Chiou WL. The Phenomenon and Rationale of Marked Dependence of Drug Concentration on Blood Sampling Site. Clinical Pharmacokinetics. 1989;17(3):175–199. doi:10.2165/00003088-198917030-00004

[49] Zanotti-Fregonara P, Chen K, Liow J-S, Fujita M, Innis RB. Image-derived input function for brain PET studies: many challenges and few opportunities. Journal of Cerebral Blood Flow & Metabolism. 2011;31(10):1986–1998. doi:10.1038/jcbfm.2011.107

[50] Bartlett EA, Ananth M, Rossano S, Zhang M, Yang J, Lin S, Nabulsi N, Huang Y, Zanderigo F, Parsey RV, et al. Quantification of Positron Emission Tomography Data Using Simultaneous Estimation of the Input Function: Validation with Venous Blood and Replication of Clinical Studies. Molecular Imaging and Biology. 2019;21(5):926–934. doi:10.1007/s11307-018-1300-1

[51] Brooks DC, Black PR, Arcangeli MA, Aoki TT, Wilmore DW. The Heated Dorsal Hand Vein: An Alternative Arterial Sampling Site. Journal of Parenteral and Enteral Nutrition. 1989;13(1):102–105. doi:10.1177/0148607189013001102

[52] Zanotti-Fregonara P, Hines CS, Zoghbi SS, Liow J-S, Zhang Y, Pike VW, Drevets WC, Mallinger AG, Zarate CA, Fujita M, et al. Population-based input function and image-derived input function for [11C](R)-rolipram PET imaging: Methodology, validation and application to the study of major depressive disorder. NeuroImage. 2012;63(3):1532–1541. doi:10.1016/j.neuroimage.2012.08.007

[53] Mabrouk R, Strafella AP, Knezevic D, Ghadery C, Mizrahi R, Gharehgazlou A, Koshimori Y, Houle S, Rusjan P. Feasibility study of TSPO quantification with [18F]FEPPA using population-based input function. PLOS ONE. 2017;12(5):e0177785. doi:10.1371/journal.pone.0177785

[54] Rissanen E, Tuisku J, Luoto P, Arponen E, Johansson J, Oikonen V, Parkkola R, Airas L, Rinne JO. Automated reference region extraction and population-based input function for brain [11C]TMSX PET image analyses. Journal of Cerebral Blood Flow and Metabolism. 2015;35(1):157–165. doi:10.1038/jcbfm.2014.194

[55] Takikawa S, Dhawan V, Chaly T, Robeson W, Dahl R, Zanzi I, Mandel F, Spetsieris P, Eidelberg D. Input Functions for 6-[Fluorine-18]Fluorodopa Quantitation in Parkinsonism: Comparative Studies and Clinical Correlations. Journal of Nuclear Medicine. 1994;35(6):955–963.

[56] Zanotti-Fregonara P, Liow J-S, Fujita M, Dusch E, Zoghbi SS, Luong E, Boellaard R, Pike VW, Comtat C, Innis RB. Image-Derived Input Function for Human Brain Using High Resolution PET Imaging with [11C](R)-rolipram and [11C]PBR28 Gelovani J, editor. PLoS ONE. 2011;6(2):e17056. doi:10.1371/journal.pone.0017056

[57] Meechai T, Tepmongkol S, Pluempitiwiriyawej C. Partial-volume effect correction in positron emission tomography brain scan image using super-resolution image reconstruction. The British Journal of Radiology. 2015;88(1046):20140119. doi:10.1259/bjr.20140119

[58] Chen K, Bandy D, Reiman E, Huang SC, Lawson M, Feng D, Yun LS, Palant A. Noninvasive quantification of the cerebral metabolic rate for glucose using positron emission tomography, 18F-fluoro-2-deoxyglucose, the Patlak method, and an image-derived input function. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 1998;18(7):716–723. doi:10.1097/00004647-199807000-00002

[59] Lammertsma AA, Hume SP. Simplified Reference Tissue Model for PET Receptor Studies. NeuroImage. 1996;4(3):153–158. doi:10.1006/nimg.1996.0066

[60] Litton J-E, Hall H, Pauli S. Saturation Analysis in PET—Analysis of Errors Due to Imperfect Reference Regions. Journal of Cerebral Blood Flow & Metabolism. 1994;14(2):358–361. doi:10.1038/jcbfm.1994.45

[61] Compartmental Analysis of Diprenorphine Binding to Opiate Receptors in the Rat in vivo and its Comparison with Equilibrium Data in vitro - Vincent J. Cunningham, Susan P. Hume, Gary R. Price, Randall G. Ahier, Jill E. Cremer, Anthony K. P. Jones, 1991. [accessed 2023 Jun 11]. https://journals-sagepub-com.proxy3.library.mcgill.ca/doi/10.1038/jcbfm.1991.1

[62] Guo Q, Owen DR, Rabiner EA, Turkheimer FE, Gunn RN. A graphical method to compare the in vivo binding potential of PET radioligands in the absence of a reference region: application to [11C]PBR28 and [18F]PBR111 for TSPO imaging. Journal of Cerebral Blood Flow & Metabolism. 2014;34(7):1162–1168. doi:10.1038/jcbfm.2014.65

[63] Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL. Distribution volume ratios without blood sampling from graphical analysis of PET data. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 1996;16(5):834–840. doi:10.1097/00004647-199609000-00008

[64] Lodge MA, Holt DP, Kinahan PE, Wong DF, Wahl RL. Performance assessment of a NaI(Tl) gamma counter for PET applications with methods for improved quantitative accuracy and greater standardization. EJNMMI Physics. 2015;2(1):11. doi:10.1186/s40658-015-0114-3

[65] Zanzonico P. Routine Quality Control of Clinical Nuclear Medicine Instrumentation: A Brief Review. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2008;49(7):1114–1131. doi:10.2967/jnumed.107.050203

[66] Boileau I, Tyndale RF, Williams B, Mansouri E, Westwood DJ, Foll BL, Rusjan PM, Mizrahi R, De Luca V, Zhou Q, et al. The Fatty Acid Amide Hydrolase C385A Variant Affects Brain Binding of the Positron Emission Tomography Tracer [11C]CURB. Journal of Cerebral Blood Flow & Metabolism. 2015;35(8):1237–1240. doi:10.1038/jcbfm.2015.119

[67] Sipe JC, Chiang K, Gerber AL, Beutler E, Cravatt BF. A missense mutation in human fatty acid amide hydrolase associated with problem drug use. Proceedings of the National Academy of Sciences of the United States of America. 2002;99(12):8394–8399. doi:10.1073/pnas.082235799

[68] Rusjan P, Mamo D, Ginovart N, Hussey D, Vitcu I, Yasuno F, Tetsuya S, Houle S, Kapur S. An automated method for the extraction of regional data from PET images. Psychiatry Research: Neuroimaging. 2006;147(1):79–89. doi:10.1016/j.pscychresns.2006.01.011

[69] Tu Z, Mach RH. C-11 radiochemistry in cancer imaging applications. Current Topics in Medicinal Chemistry. 2010;10(11):1060–1095. doi:10.2174/156802610791384261

[70] Hidex Automatic Gamma Counter - User Guide, Version 1.8. 2020. https://hidex.com/products/hidex-automatic-gamma-counter/

[71] Boileau I, Mansouri E, Williams B, Le Foll B, Rusjan P, Mizrahi R, Tyndale RF, Huestis MA, Payer DE, Wilson AA, et al. Fatty Acid Amide Hydrolase Binding in Brain of Cannabis Users: Imaging with the Novel Radiotracer [11C]CURB. Biological psychiatry. 2016;80(9):691–701. doi:10.1016/j.biopsych.2016.04.012

[72] Best LM, Hendershot CS, Buckman JF, Jagasar S, McPhee MD, Muzumdar N, Tyndale RF, Houle S, Logan R, Sanches M, et al. Association Between Fatty Acid Amide Hydrolase and Alcohol Response Phenotypes: A Positron Emission Tomography Imaging Study With [11C]CURB in Heavy-Drinking Youth. Biological Psychiatry. 2022 Dec:S0006322322018042. doi:10.1016/j.biopsych.2022.11.022

[75] Doğan NÖ. Bland-Altman analysis: A paradigm to understand correlation and agreement. Turkish Journal of Emergency Medicine. 2018;18(4):139–141. doi:10.1016/j.tjem.2018.09.001

[76] Pain F, Laniece P, Mastrippolito R, Gervais P, Hantraye P, Besret L. Arterial Input Function Measurement Without Blood Sampling Using a ␤-Microprobe in Rats.

[77] Lodge MA, Holt DP, Kinahan PE, Wong DF, Wahl RL. Performance assessment of a NaI(Tl) gamma counter for PET applications with methods for improved quantitative accuracy and greater standardization. EJNMMI Physics. 2015;2(1):11. doi:10.1186/s40658-015-0114-3

[78] Fowler JS, Logan J, Wang G-J, Volkow ND, Telang F, Ding Y-S, Shea C, Garza V, Xu Y, Li Z, et al. Comparison of the binding of the irreversible monoamine oxidase tracers, [11C]clorgyline and [11C]l-deprenyl in brain and peripheral organs in humans. Nuclear Medicine and Biology. 2004;31(3):313–319. doi:10.1016/j.nucmedbio.2003.10.003

[79] Jafari-Khouzani K, Paynabar K, Hajighasemi F, Rosen B. The effect of region of interest size on the repeatability of quantitative brain imaging biomarkers. IEEE transactions on bio-medical engineering. 2019;66(3):864–872. doi:10.1109/TBME.2018.2860928

[80] Hasford F, Wyk BV, Mabhengu T, Vangu MDT, Kyere AK, Amuasi JH. Effect of Radionuclide Activity Concentration on PET-CT Image Uniformity. World Journal of Nuclear Medicine. 2016;15(2):91–95. doi:10.4103/1450-1147.167578