Diprenorphine (mu delta kappa antagonist) at two, seven and 24 hours post drug. To optimize the quantification we employed various region of interest (time activity curves) and parametric (using SRTM) reference region modeling methods (REFM) employing the occipital cortex as the reference region. Occupancy measures during the two, seven and 24 hours post drug demonstrated a peak of 90% declining to 85% occupancy with no significant difference between the REFM measures at each time point. To confirm using the more traditional approach with a radial arterial input, various one and two tissue compartment models were considered. Occupancy estimated by arterial methods compared to REFM methods was within 10% for the two methods measured at two and seven hours post drug. This demonstrates the approach of serial measures of opiate receptor occupancies of initial dosing and washout for potential future therapeutic dose selection with opiate drugs. It emphasizes the importance of verifying the appropriate mathematical models for quantification of the outcome measures depending on whether methodological accuracy (e.g. using arterial input and specific compartment models) or simpler logistics (e.g. with REFM techniques) are required for drug development decisions.

No. 117

SYNTHESIS, RADIOLABELING AND EVALUATION OF 4-METHOXY-1H-INDOLE-3-CARBOXYLIC ACID-(4-[4-(2,4-DICHLORO-PHENYL)PIPERAZIN-1-YL]BUTY))AMIDE ([11C]WLD3.001) AS DEVELOPMENT OF POTENTIAL SELECTIVE DOPAMINE D3 POSITRON EMISSION TOMOGRAPHY TRACER

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Introduction: Antagonism of the dopamine D3 receptor was suggested to be important to the therapeutic effects of antipsychotic drugs. To date the vast majority of dopamine receptor radiotracers are nonselective binding to both D2 and D3 subtypes, complicating interpretation of results. To address this issue, we synthesized [C-11]WLD3.001 and performed an initial assessment of its potential as a selective D3 receptor positron emission tomography (PET) tracer. Methods: WLD3.001 and its corresponding phenol precursor WLD3.002 were synthesized. The Log P value of WLD3.001 was assessed by an HPLC method, and *in vitro* binding assays performed. [C-11]WLD3.001 was synthesized by reacting WLD3.002 with [C-11]CH3I at 40 C for two minutes. Regional brain biodistribution and blocking studies were performed in conscious male Sprague - Dawley rats (225-300g). Results: The affinities (Ki) of WLD3.001 for dopamine D2, D3, D4 and D5 subtypes were 1,650 nM, 2.4 nM, 2,818 nM and >1000 nM, respectively. The log P value was 2.92. The regional brain biodistribution data revealed that peak uptake (%ID/g +/- SD) at 15 minutes post-injection were highest in the thalamus (0.96 +/- 0.10) > frontal cortex (0.84 +/- 0.07) > striatum (0.67 +/- 0.10) > cerebellum (0.49 +/- 0.03), with clearance of activity from all regions thereafter. Blocking studies (15 minutes) revealed ~45% saturable binding in the thalamus and frontal cortex, and ~25% specific binding in other regions. Conclusions: [C-11]WLD3.001 is a high affinity selective ligand for dopamine D3 receptors that exhibited saturable binding in the rodent brain. Further characterization of this tracer is warranted.

No. 118

DCE MAGNETIC RESONANCE IMAGING DETECTED DIFFERENTIAL RESPONSE OF METASTATIC VERSUS INDOLENT HUMAN MELANOMA TO ZD6126 TREATMENT

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It has been previously demonstrated that two melanoma cell lines obtained from a surgically excised tumor of the same patient have different phenotype: C6181cells form a metastatic tumor *in vivo* when xenografted in nude mice; microscopic necrosis or a necrotic center is common in this tumor; it even forms blood vessels through a unique mechanism called vasculogenic mimicry. On the other hand, the indolent line (A375P) is not metastatic. ZD6126, which targets the microtubular cytoskeleton of endothelial cells, is shown to induce vascular shutdown leading to tumor necrosis. We hypothesized that metastatic melanoma may have more immature vasculature, which can be blocked by ZD6126 treatment. We utilized dynamic contrast enhanced (DCE) magnetic resonance imaging (MRI) to study the acute response (within one hour after treatment). The pretreatment Ktrans values (first order rate constant for transfer of contrast agent from vasculature to tumor interstitium) of C8161 and A375P are 0.45 (±0.29, n=5) min-1 and 0.15 (±0.11, n=4) respectively. Immunostaining for CD31 shows that C8161 has higher vessel fraction than the A375P tumor (4.5% vs 2.2%, $P<0.05$). A significant reduction of Ktrans (0.16 min-1 compared to the pretreatment value of 0.45 min-1, $P<0.05$) in C tumors was observed within an hour after injection of ZD6126 (200 mg/kg), whereas Ktrans was reduced only slightly in A tumors ($P=0.1$) in response to ZD6126 treatment. Our results suggest that a radical difference in vasculature between the two melanomas could be the mechanism behind this differential response and DCE MRI could play a critical role in probing this difference.

Poster Presentations

Basic Science Poster Presentations

No. 119

EFFECT OF SINOGRAM FILTERING IN THE QUALITY OF POSITRON EMISSION TOMOGRAPHY RECONSTRUCTIONS

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Introduction and rationale: In the reconstruction of positron emission tomography (PET) studies, list mode data are usually aggregated into sinograms. This step is necessary for filtered backprojection algorithms and also for some statistical methods. Several effects, such as randomness of the positron emission, scatter, positron range and non-colinearity, degrade these sinograms. The subsequent reconstruction process propagates these errors to the final images. Since filtering in the angular direction introduces non-uniform tangential blurring, sinograms are generally filtered only in the radial direction for noise reduction. This filtering, however, also degrades resolution. Several methods have been proposed to face this problem, for instance filtering in the Wavelet or Stackgram domains. Fourier transform of a sinogram is known to show a particular shape of the spectral energy distribution. In this work, this property has been exploited to perform an adapted filtering, comparing the results with previously reported methods. Materials and methods: Data from phantoms and rodents obtained from a real PET system (rPET, SUINSA) have been used to compare different sinogram filtering techniques and to evaluate the enhancement achieved. Results and conclusions: A comparison of different methods for noise reduction in sinograms is presented. The proposed method for filtering in the Fourier domain provided the best results in terms of efficiency, noise reduction and simplicity. It achieved a SNR increase of up to 30% with no FWHM degradation. Furthermore, this correction improves the sinogram leading a visual enhancement similar to that of scatter correction methods.

No. 120

EFFECT OF MISALIGNMENTS IN SMALL ANIMAL POSITRON EMISSION TOMOGRAPHY SCANNERS BASED ON ROTATING PLANAR DETECTORS

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Introduction: Technological advances have improved the assembly process of positron emission tomography (PET) devices, resulting in quite exact geometric parameters. However, in high sensitivity and high spatial resolution systems, even minimum misalignments (submillimetric) of the

detectors may result in a noticeable degradation of the image resolution. For this reason, in such systems an exact characterization of misalignments is critical for a good reconstruction quality. While this subject is widely studied for computed tomography (CT) and single photon emission computed tomography (SPECT) systems based on cone beam geometry, it seems that this is not the case for PET scanners based on rotating planar detectors. The purpose of this work is to analyze misalignment effects in these systems and to define a protocol for geometric characterization. Materials and methods: The effects of misalignments have been simulated and the results have been validated with data from a real scanner (rPET, SUINSA), using both phantom and rodent studies. Results and conclusions: The effects of detector misalignments are presented. A testing protocol for detecting and measuring misalignments in the three axes in PET scanners based on rotating planar detectors is proposed. This protocol uses simple phantoms and is robust and easy to perform. Implementation details are given for the high-resolution animal rPET scanner. The results show the importance of detector alignment: for instance, a misalignment of 0.8 mm in one detector resulted in an increase of 14% in tangential FWHM of a point source in the center of field-of-view (FOV). The correction performed with the proposed protocol provided a significant improvement in resolution.

No. 121

ISSUES IN THE QUANTITATIVE RECONSTRUCTION OF POSITRON EMISSION TOMOGRAPHY STUDIES

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Introduction: In order to make quantitative analysis of positron emission tomography (PET) studies it is necessary to obtain an "exact" reconstructed image. This is not trivial to obtain as each step in the process from list mode data can be a source of bias or artifacts. Sinogram statistical distribution may be altered due to the acquisition process: scatter, decay, dead time, geometrical effects and crystal sensitivity. Subsequent sinogram rebinning may also change this statistical distribution. Finally, FBP may introduce DC component bias and aliasing, depending on the particular implementation used. This work analyzes the whole process to ensure that all these undesirable effects are properly compensated at every point of the reconstruction chain to guarantee a true quantitative reconstruction. Materials and methods: The study of quantitative reconstruction was applied to a real scanner (rPET, SUINSA). Different theoretical and experimental methods were tested for sinogram correction. Several methods for SSRB statistics recovery and for count recovery and aliasing elimination after FBP were tested. Results were validated on real data using a NEMA-like contrast phantom, considering attenuation and scatter. The linear behavior of detected trues versus activity in the field-of-view was verified. Results and Conclusions: A complete reconstruction algorithm for the rPET system is presented. An experimental correction of the sinogram based on an acquisition of a field flood provided best results. Counts recovering in the SSRB step and adequate slice uniformity have been achieved. Regarding FBP implementation, the Crawford method was selected for compensating DC bias and aliasing after filtering in Fourier domain.

No. 122

STATISTICAL PARAMETRIC MAPPING IN SMALL ANIMAL BRAIN ACTIVATION STUDIES

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Ultra-high resolution positron emission tomography (PET) has enabled the visualization of biochemical processes in the brain in small animals, and changes due to disease or stimuli. Conventional analysis methods using manually-drawn regions-of-interest (ROIs) to extract counts are highly subjective, and it is difficult to identify subregions of the brain. Pixel-based analysis, such as statistical parametric mapping, perform automated analysis of brain images to detect differences within or between groups. This work describes the application of pixel-based analysis to an 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) brain activation study in rats. A total of seven rats were scanned 45 minutes after injection of FDG. Each animal received two randomized scans, one with vibrissae stimulation for 15 minutes during the uptake phase of FDG, the other with no stimulation as a control. The brains were extracted from the PET images using a region-growing method, and coregistered to each other using a mutual information algorithm. Stimulated and unstimulated images were compared using pixel-by-pixel paired t-tests to determine statistically significant differences ($p<0.01$). Clusters of significant pixels were further assessed to compensate for correlated multiple comparisons (corrected $p<0.05$). Statistically significant regions were compared against conventional ROI analysis. Different methods of normalization, using either whole brain or cerebellum counts, were tested. Contralateral somatosensory cortices were activated by the vibrissae stimulation, with increased FDG uptake. Both pixel-based and ROI analyses agreed in the regions affected by the activation. Only cerebellar normalization gave the expected hypermetabolic regional differences, while whole brain normalization produced hypometabolism in regions that should be unaffected.

No. 123

SIMPLIFIED QUANTIFICATION OF SMALL ANIMAL 2-DEOXY-2-[F-18]FLUORO-D-GLUCOSE- POSITRON EMISSION TOMOGRAPHY STUDIES USING A STANDARD ARTERIAL INPUT FUNCTION

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Arterial input function (AIF) measurement for quantification of small animal positron emission tomography (PET) studies is technically challenging and limited by the small blood volume of small laboratory animals. The present study investigates the use of a standard arterial input function (SAIF) to simplify the experimental procedure. Methods: Twelve 2-deoxy-2-[F-18]fluoro-D-glucose (FDG)-PET studies accompanied by serial arterial blood sampling were acquired in seven male Sprague-Dawley rats under isoflurane anesthesia without (every rat) and with additional (five rats) vibrissae stimulation. A leave-one-out procedure was employed to validate the use of a SAIF with individual scaling by one (1S) or two (2S) arterial blood samples. Results: Automatic slow bolus infusion of FDG resulted in highly similar AIF in all rats. The average difference of the area under curve of the measured AIF and the individually scaled SAIF was $0.11 \pm 4.26\%$ and $0.04 \pm 2.61\%$ for the 1S (six-minutes sample) and 2S (four-minutes/43-minutes samples) approach, respectively. The average difference between the cerebral metabolic rates of glucose (CMR_{glc}) calculated using the measured AIF and the scaled SAIF were $1.31 \pm 5.45\%$ and $1.30 \pm 3.84\%$ for the 1S and 2S approach, respectively. Conclusions: The use of a SAIF scaled by one or (preferably) two arterial blood samples can serve as a valid substitute for individual AIF measurements to quantify FDG-PET studies in rats. The SAIF approach minimizes the loss of blood and should be ideally suited for longitudinal quantitative small animal FDG-PET studies.

No. 124

BIOLUMINESCENCE IMAGING CONFIRMS THAT WEEKLY COMPUTED TOMOGRAPHY STUDIES DO NOT CHANGE TUMOR GROWTH IN AN ANIMAL MODEL OF BREAST CANCER METASTASIS

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The use of X-ray computed tomography (CT) to monitor tumor growth in animal models is becoming widespread. The purpose of this study was to determine whether X-ray exposure would change metastatic tumor development in an animal model. Methods. Female BALB/c nude mice