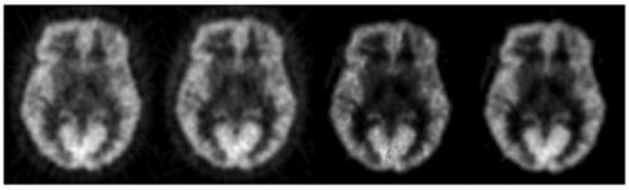
P143. Test-retest reliability of [^{11}C]flumazenil data acquired using the Delforge partial saturation method

S. Bouvard[1,2], N. Costes[2], F. Bonnefoi[2], F. Lavenne[2], F. Mauguière[3], P. Ryvlin[1] and A. Hammers[3]

[1]Translational and Integrative Group in Epilepsy Research, Lyon Neuroscience Research Center, CNRS 5292, INSERM U1028, Lyon, France; [2]CERMEP-Imagerie du vivant, Lyon, France; [3]Neurodis Foundation, Lyon, France; [4]Department of Functional Neurology and Epileptology and Institute for Children and Adolescents with Epilepsy (IDEE), Hospices Civils de Lyon, Lyon, France

Background: [^{11}C]flumazenil (FMZ) PET images $GABA_A$ receptors. Various methods of data analysis are used in the literature, including simple summed radioactivity images (SRI) and parametric images, obtained via compartmental modelling with or without an arterial input function, or via spectral analysis. The Delforge partial saturation method (1997) has been used extensively but no test-retest data on the reliability of the various possible output images has been available.
Methods: Ten healthy controls (22-47 years) were studied twice at one-week intervals. All had high resolution 1.5T MRI. After injection of 2.6 MBq/kg of [^{11}C]FMZ and 0.01 mg/kg of unlabeled FMZ, 3D data were acquired on a Siemens/CTI ECAT HR+ over 55 m, corrected for attenuation and scatter, and rebinned into 12 time frames. SRIs were created over two published time intervals (10-20 m, SRI-10-20, and SRI-20-45). Both were also expressed as standardized uptake values (SUV; SUV-10-20; SUV-20-45). The partial saturation model, based on a Scatchard plot, was used for the calculation of parametric Bmax images, with pons as a reference and with Kd either variable per voxel (BmaxKdvar) or using the same Kd throughout (BmaxKdfix). 83 regions were sampled with a frequency-based brain atlas (Hammers et al., 2003) warped onto each individual's MRI scan using Statistical Parametric Mapping software (SPM5), thresholded at 50% grey matter probability, and then coregistered onto each individual PET. Image quality was assessed visually. Average percentage test-retest differences were calculated as the standard deviation of (test-retest)/mean (test + retest) for all grey matter containing regions except pallidum and those under ten times scanner resolution ($\sim 4.1^3$ mm^3). Reliability was assessed per region via the intraclass correlation coefficient (ICC).



Figure

Results: Image quality was good for all types (Figure). The rank order of % test-retest differences (absolute values) was SUV-20-45 > SRI-20-45 > BmaxKdvar > SRI-10-20 > SUV-10-20 > BmaxKdfix. The rank order of ICCs was similar.
Conclusions: Considering left and right regions separately and including some regions with low binding (e.g. basal ganglia) may explain somewhat worse values than in other test-retest studies. Bmax is in theory an attractive parameter to quantify, being directly related to receptor concentration. However, in our hands Bmax parametric maps had relatively high test-retest variability and low reliability, with hardly any regions achieving ICCs considered as good, i.e. > 0.70. We did, however, not test the reliability of measures of Bmax derived directly from less noisy time-activity curves at the ROI level. SRI and SUV images obtained between 20 and 45 m post injection performed best, with good ICCs despite relatively high average test-retest variability ($\sim$10%). SRI-10-20 and SUV-10-20 images had intermediate values, unlikely to be sufficient for most studies (compare e.g. Hammers et al. 2008).

Reference

Hammers, A. et al., *J Cereb Blood Flow Metab* 2008; 28(1):207-16.

P144. PETmodel: an SPM toolkit for parametric imaging of dynamic PET data

Christopher J. Endres[1], Yun Zhou[2], Hassan Mohy-Ud-Din[2] and Arman Rahmim[2]

[1]Dept of Radiology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA; [2]Dept of Nuclear Medicine, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA

Background: A crucial step towards the application of statistical parametric mapping (SPM) techniques to PET is the generation of parametric images from dynamic PET data. Unfortunately, there currently is

no widely distributed toolkit incorporated into SPM that performs parametric modeling. Instead, investigators typically write custom modeling software that may be used exclusively at a single institution or even in an individual lab. In addition to being time-consuming to write the code, the existence of numerous software tools makes it likely that there are subtle differences and inconsistencies in the application of parametric models across research institutions. In order to promote the consistent application of such models, it would be far more expedient to have a toolkit that can be operated directly from the SPM menu to take advantage of the built in user interface and batch utilities. The freely available open source code distribution of a parametric PET modeling SPM toolkit, along with the expected frequent usage, would allow for rapid testing, debugging, and expansion of models/capabilities. In addition to promoting consistency in the application of specific models, incorporation into SPM would also allow the modeling to be streamlined in a batch job. Such implementation would allow investigators to test and apply models that they may not be familiar with and thus would otherwise not attempt. The numerous parametric modeling methods that are in common use should ideally be available freely to all PET investigators, and the PETmodel SPM toolkit aims to fulfill that need.

Methods: The basic design of the PETmodel SPM toolkit is as follows: **Inputs** - As per the SPM convention, dynamic PET data may be either a single 4D Nifti format image volume OR a sequence of 3D Nifti format image volumes. In addition, most models will typically require two text files containing the input function and the PET frame times, respectively. Both text files are in a two-column format. **Outputs** - Depending on the model, 2-3 parametric images will be written separately in Nifti format. For example, slope and Intercept images would be generated when applying conventional graphical methods.
Results: Models - The initial implementation supports several common models including Logan, Patlak, MRTM, and MRTM2. For formal release of the toolkit it is also planned to include LRRSC, SRTM2, the relative equilibrium as well as bi-graphical methods. The basis function approach will be added in the near future. **Operation** - PETmodel will be provided as an SPM8 toolkit and will appear as an option under the PET/SPECT toolbox menu. The entry dialogue will follow the SPM convention.
Conclusions: PETmodel is an SPM compatible open source Matlab toolkit that will be made freely available and will help to standardize application of PET parametric imaging methods.

P145. Optimal design in PET occupancy studies: a sensitivity study

Mattia Veronese[1], Stefano Zamuner[2], Roger N. Gunn[3] and Alessandra Bertoldo[1]

[1]Department of Information Engineering, University of Padova, Padova, Italy; [2]Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, Stockley Park, UK; [3]Imanova Limited, London, UK; Imperial College, London, UK

Background: The application of optimal design algorithms to pharmacokinetic/pharmacodynamic experiments allows parameters to be estimated with minimum bias and variance [1]. In PET receptor occupancy (PET-RO) [2] studies it has been demonstrated that adaptive optimal design (AOD) algorithms allow a reliable selection of experimental design variables, such as dose levels or scan times post dose [3]. However the value of applying adaptive or non-adaptive optimal design methodologies to PET-RO studies depends on several factors including drug affinity to the target as well as feasibility constraints, such as sample size, number of scan per subjects and logistical constrains.
In this work we presented a simulation study to evaluate the sensitivity of PET-RO studies to experimental scanning times. We also investigated the potentialities of optimal design algorithms when applied to PET-RO in presence of mis-specified drug kinetic assumptions.
Methods: A population k_{on}-k_{off} model relating the plasma concentration of the drug and the PET binding potential (BP) was applied to generate simulated data. Inter-subject variability was defined by an exponential distribution model (coefficient of variation, CV 30%), while noisy BP measures were simulated by assuming a proportional error model for the residual variability (CV 10%). Simulated experimental designs were chosen according to different levels of parameter mis-specifications with respect to the true simulated values (range: [-300%; +300%]). For each design, 100 populations each with 12 subjects were considered. Only two PET scans after baseline were assumed per subject, chosen in a time window of 0-36 hours (minimum distance 4 hours). Analysis of the results included a comparison of the performance of adaptive, non-adaptive optimal designs and non-optimized designs. Design optimization was identified using the D-optimality criterion [4]. Three simulated compounds with different brain affinities (low, medium and high) were tested, with $K_d (= k_{off}/k_{on})$ equal to 15, 2.5 and 0.25 respectively . The dose level was held constant for all the simulations.