ADVANCING PET SCIENCE FOR
NEW MEASURES OF BRAIN FUNCTION

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ABSTRACT

This project has continued the development of new chemistry and imaging physics applicable to PET studies of the human brain. In basic radiochemistry research, we have developed a modified approach to solid-phase supported [^{11}C]methylation system, in part dependent on the design, fabrication and validation of new small, sensitive and accurate positron detectors useful in tracking the flow of radioactivity through the synthesis apparatus. Radiopharmaceutical efforts have resulted in synthesis of new tracers of mitochondrial enzymes. For evaluation of new PET radiotracers, we have applied new models of unilateral brain lesions using quinolinic acid and MPP+, as models of neurodegenerative diseases. In the physics and data analysis research area we have developed faster and more accurate means of performing image reconstruction for use with both emission and transmission data. We are optimizing acquisition and kinetic modeling strategies for new radiotracers. We also have implemented and proven the utility of performing task switching during PET CBF activation studies for the purpose of enhancing signal-to-noise and greater detectability of areas of activation. We are also working on routines for standardization of analysis strategies for group vs. group and individual vs. group comparisons.

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Project 1 Radiochemistry (Drs. Kilbourn, Jewett and Charalambous)

As part of our overall radiochemistry program aimed at new methods for production and evaluation of PET radiopharmaceuticals, this Department of Energy grant has supported progress in a number of diverse but inter-related areas.

Radiochemical Methods (Dr. Jewett)***Development of an improved microreactor for carbon-11 radioalkylations (Project 1A, Specific Aim 2, D. Jewett)***

We have made substantial progress in this period in the development of a microreactor which should be widely applicable to carbon-11 radioalkylations with either [^{11}C]methyl triflate or [^{11}C]methyl iodide. Because of the need to develop a practical synthesis of [^{11}C]dihydrotrabenazine (DTBZ) we simplified and improved the captive solvent system which we originally applied successfully to [^{11}C]flumazenil. However, while this has resulted in a very simple, reliable system for DTBZ, it still lacks the general applicability we had sought. Because of the clear advantage of doing radioalkylations in small columns we have continued to try many different approaches. The development of small positron-specific detectors by our group has allowed us to take a completely new approach.

In the captive solvent method, [^{11}C]methyl iodide (or [^{11}C]methyl triflate) is passed through a small column containing the substrate in an appropriate solvent adsorbed on a porous support. The system must be sufficiently reactive so that the reaction occurs on first pass. Sometimes heating is required, but this may lead to side-reactions. Thus there is a trade-off between the radiochemical yield and the specificity of the labeling reaction. In the system we have now developed this trade-off has been eliminated as follows: The system allows the reaction column to be cooled as low as $-70\text{ }^{\circ}\text{C}$ then heated rapidly to any desired temperature. During a radiosynthesis the column is cooled sufficiently so that all of the [^{11}C]methyl triflate or [^{11}C]methyl iodide is trapped on the column. The flow path is then switched so that the column is in a loop with a peristaltic pump. The column is heated to the desired temperature, and the pump circulates the [^{11}C]methyl iodide (or [^{11}C]methyl triflate) over the column continuously until the reaction is essentially complete. A positron-sensitive detector in the circuit allows the disappearance of the volatile radiolabel to be monitored. With a multiple-pass system exposure of the substrate to the volatile label is efficient, and the column can be maintained at a lower temperature.

In addition to its applicability in the production of carbon-11 radiopharmaceuticals such a system may prove to be a unique tool for the development of new carbon-11 agents. With the batch reactors usually used for radiomethylations it is hard to get information about the rate of the reaction. As a result most reaction systems are probably far from optimal. This system should allow more efficient selection of solvents, bases and reaction conditions when new agents are developed.

Before the method can be applied to practical radiopharmaceutical production two technical problems must be better solved. First, simple instrumentation for monitoring the output of the positron-sensitive detector must be available so that it doesn't introduce any complexity to the system or to the labeling procedure. Secondly, although a peristaltic pump for circulating the

[^{11}C]methyl triflate or [^{11}C]methyl iodide is desirable from the standpoint of simplicity, it is hard to find a type of tubing that is unreactive toward [^{11}C]methyl triflate and still highly flexible.

Development of sensitive positron detectors for radiochemical apparatus

We have designed and built a flow-through positron sensitive detector to aid radio chemists in developing synthetic techniques and to facilitate apparatus troubleshooting in real-time. The detectors small size and insensitivity to 511 KeV gamma's enable them to be installed in-line between reaction vessels without need for additional shielding or any other special considerations.

The detectors utilize a trapezoidal shaped (10mm short leg x 11.6mm tall x 23.4mm long leg x 10mm thick) plastic scintillator optically coupled to a large area (10mm x 10mm) photo diode. The scintillator dimensions were chosen to be sufficient to capture the common PET isotopes positrons and its shape to maximize scintillated light collection. A hole through the center of the trapezoid accommodates a piece of standard 1/16" OD plastic tubing that is usually fitted with 1/4-28 end fittings and is then connected between two vessels in the apparatus. The photo diode is operated in photovoltaic mode by a two stage high impedance low current amplifier capable of operating most lab recorders and all A/D converters for computer capture of data sets.

Tests to date indicate three orders of magnitude range of linear operation as well as predicted sensitivity to isotope positron energy.

Radiopharmaceutical Development (Drs. Kilbourn and Charalambous)

Inhibitors of Mitochondrial Complex I

We have begun a program aimed at the synthesis and evaluation of high affinity inhibitors of the complex I of mitochondria. Synthetic efforts have resulted in the production of two high specific activity radioligands, [^{11}C]rotenone and [^{11}C]dihydrorotenol. Animal studies with these radioligands has commenced (described in a following section) and have been very encouraging.

Positron-emitter labeled free radical spin traps

We have utilized our expertise in fluorine-18 labeling (previous DOE-supported research) to develop a rapid synthesis of a fluorine-18 labeled free radical spin trap, N-tert-butyl-a-(4-[^{18}F]fluorophenyl)nitron ([^{18}F]FPBN). This has been prepared in moderate yields in a rapid, continuous flow synthesis system, with the product isolated in high chemical and radiochemical purity. This radiotracer is now available for studies of free radical production in animal models of degenerative disease (see following section).

Animal Models in Radiopharmaceutical Evaluations (Project 1C; Drs. Kilbourn and Charalambous))

Gerbil Stroke Models

As part of the project to evaluate radiolabeled spin traps such as [^{18}F]FPBN (see above), we have implemented the unilateral gerbil occlusion model. In this model, one carotid artery of the gerbil is transiently occluded, producing ischemia on one side of the brain; the length of time of occlusion can be varied. This allows side-to-side comparisons of radiotracer uptake and retention.

This model will now be available to study the effects of brain ischemia on free radicals, mitochondrial enzymes, proteases, receptors and neurotransmitter transporters, all of which are being developed in this radiochemistry program.

Unilateral neurotoxin models of disease

In the past, we have utilized unilateral injections of 6-hydroxydopamine to create animal models of Parkinson's disease. In the last months, we have initiated studies with two new types of unilateral neurotoxin models of human disease.

First, we have utilized unilateral striatal injections of quinolinic acid, a neurotoxic excitatory amino acid. The quinolinic acid injections have been proposed by others as a model of Huntington's disease. We have utilized this model in the evaluation of [^{11}C]rotenone, and demonstrated a unilateral decrease in radiotracer binding in the injected striatum, consistent with neuronal loss. This was not due to blood flow reductions, as we determined simultaneously the regional brain blood flow using the agent [$^{99\text{m}}$]TcHMPAO. The reduction in rotenone binding also greatly exceeded the reductions in [^{18}F]FDG uptake in the affected striatum, indicating a dissociation between the mitochondrial enzymatic activity and glucose metabolism.

Second, we have developed and utilized intra-striatal injections of MPP+, a neurotoxin specific for the mitochondrial complex I enzymatic site. Using this model, we have been able to demonstrate that the loss of [^{11}C]rotenone or [^{11}C]rotenol binding in the injected striatum was due to binding of the radioligands to complex I. This animal model will be of considerable use in the evaluation of the radiolabeled rotenoids, as well as in the study of what subsequent biochemical parameters (glucose metabolism, neurotransmitter receptors, transporters) are affected following complex I inhibition. This area is of great current interest and controversy, due to the proposals that mitochondrial energy metabolism disruptions are at the root of many degenerative neurological diseases.

PET evaluation of gene transfer technology

In a new collaboration with investigators involved in human gene transfer therapy, we have utilized PET to evaluate effects of intra-cerebral injections of vectors (virus + gene) in primates. For these studies, two monkeys were given unilateral striatal injections of adenovirus vector, one carrying a gene encoding the enzyme HPRT (hypoxanthine-guanine phosphoribosyltransferase). HPRT is believed to be involved in the development of Lesch-Nyan disease, through involvement of the dopamine system. Animals were PET scanned using [^{11}C]raclopride and [^{18}F]FDG at times prior to virus injection, and 1, 3 and 6 weeks after injection.

As expected and hoped for, there were no changes in the PET scans of either monkey, demonstrating that the adenovirus injections did not cause tissue damage in the brain. As these were normal monkeys, no alterations were expected in the [^{11}C]raclopride scans, as the addition of more HPRT should not have altered the normal production of dopamine.

This is an exciting, entirely new area of research, which brings together the fields of PET imaging and molecular biology.

Improvement of resolution of animal PET scanner

To improve our abilities to utilize the PCT 4600 PET scanner for animal experiments, we have (in collaboration with the Physics group of Dr. Koepp) undertaken physical modifications of the scanner. This has been successful, resulting in improved in-plane resolution by modifications of the addition of foam-supported lead inserts, although at the cost of reduced sensitivity. However, as we do not have limitations on the amounts of activity injected in animals, this can be overcome by injection of higher doses of PET agents.

The scanner was modified by occlusion of a certain portion of the physical dimension of the round detector face. After several iterations (fabrication of lead inserts and testing of scanner performance) a design that utilized asymmetrically shaped lead pieces mounted in donut shaped foam rings was adopted. The 96 lead pieces per ring were formed into "house" shaped pieces being 25mm tall x 11mm wide x 20mm deep with a 15° slope to the "roof". When properly positioned this design allowed each detector to be blocked on its radial edge while still maintaining a full view in its axial direction. The resulting changes in scanner specifications are shown in comparison in the following table.

PARAMETER	OLD	NEW
Resolution (on axis)		
- Direct (mm)	10.9	7.0
- Cross (mm)	--	8.2
Resolution (off axis)		
- Direct (mm)	11.0	7.7
- Cross (mm)	--	8.6
Sensitivity		
-Direct(kcps/mCi/ml)	19.8	5.4
-Cross(kcps/mCi/ml)	29.8	8.6
Scatter		
- Direct (%)	17.3	15.7
- Cross (%)	--	14.8
Axial Resolution(mm)	9.1	9.0

Publications

- DaSilva JN, Kilbourn MR, Carey JE, Sherman P and Pisani T: Characterization of [^{11}C]tetrabenazine as an in vivo radioligand for the vesicular monoamine transporter, Nucl Med Biol 1994; 21; 151-156.
- Van Dort ME, Kilbourn MR and Mangner TJ: Synthesis of N-{N-[4-(4-{N-[^{11}C]methylamino}phenyl)butyryl]-l-prolyl}pyrrolidine: a potential radiotracer for prolyl endopeptidase, J Labeled Compds Radiopharm 1994;34; 447-452.
- Charalambous A, Mangner TJ and Kilbourn MR: Synthesis of (N-[^{11}C]methyl)Y-29794, a competitive inhibitor of prolyl endopeptidase, J Labeled Compds Radiopharm 1994;34; 499-503.
- Mulholland GK, Kilbourn MR, Sherman P, Carey JE, Frey KA, Koeppe RA and Kuhl DE, Synthesis, in vivo biodistribution and dosimetry of [^{11}C]N-methylpiperidyl benzilate ([^{11}C]NMPB), a muscarinic acetylcholine receptor antagonist, Nuclear Medicine and Biology, in press
- Charalambous A, Mangner TJ and Kilbourn MR: Synthesis of (2-[^{11}C]methoxy)rotenone, a marker of mitochondrial complex I activity, Applied Radiation and Isotopes, in press
- Kilbourn MR: PET radioligands for vesicular neurotransmitter transporters, Med Chem Res. , submitted
- Bormans G and Kilbourn MR, Synthesis of N-tert-butyl-a-(4-[^{18}F]fluorophenyl)nitron ([^{18}F]FPBN) for in vivo detection of free radicals, J Labeled Compds Radiopharm, submitted
- Charalambous A, Tluczek L, Frey KA, Greenamyre TJ and Kilbourn MR: Synthesis of (2-[^{11}C]methoxy)-6',7'-dihydrototenol, a second generation rotenoid for marking mitochondrial complex I activity, Nucl Med Biol, submitted

Project 2: PET Physics and Data Analysis (Drs. Koeppe, Fessler and Minoshima)

As part of our overall PET Physics program aimed at the improvement in quantification of PET data, this Department of Energy grant has supported progress in the following areas outline below.

Reconstruction Methods (Dr. Fessler)

During the past project period in this subproject (2B) we have focussed on developing, analyzing, and implementing faster converging statistical image reconstruction algorithms for both emission and transmission scans.

Emission tomography

For iteratively reconstructing emission images, we have previously developed a coordinate-descent algorithm that minimizes a penalized weighted least-squares (PWLS) objective function (Fessler, 1994a). This method is particularly suited to PET data that has been precorrected for random coincidences, which has been our standard protocol. That precorrection introduces negative values into the sinogram, and invalidates the Poisson statistical model that is the basis for the increasingly popular estimate-maximize (EM) algorithm. We have recently improved the convergence rate of the PWLS method by introducing an under-relaxation parameter, which accelerates convergence to about 10 iterations. On a DEC 3000 model 800, we can process one frame of 15 slices for the ECAT 931 scanner in 6 minutes, and one frame of 47 slices for the ECAT 921 scanner in 14 minutes. This method is also being used for cardiac SPECT imaging (Ficaro et al, 1994). To our knowledge, this is the fastest converging iterative emission reconstruction method currently available. We have also shown that the PWLS method is statistically more accurate than the truncated singular value decomposition (SVD) method (Fessler and Hero, 1994b).

With the system 7.0 software soon to arrive from Siemens/CTI, it will become easier to acquire separate prompts and delayed sinograms, so that the Poisson nature of the raw data can be preserved. Therefore, we have also developed improved iterative algorithms for the Poisson statistical model. We have analyzed the reason for the slow convergence of the EM algorithm: it is based on an inefficient choice for the "complete data space" which is used in its derivation (Fessler and Hero, 1994a; Hero and Fessler, 1994a). With this understanding, we have developed an extension of the EM algorithm, called the "space alternating generalized EM (SAGE) algorithm," (Fessler and Hero, 1994a; Fessler, 1994b) which uses more efficient choices for the complete data space. Whereas the EM algorithm requires hundreds of iterations to converge, the SAGE algorithm typically requires only about 20 iterations. This significant improvement in convergence rate brings iterative methods based on the Poisson model closer to being feasible for routine work. However, the SAGE algorithm still requires more computation than the PWLS method described above, which is effectively based on an inhomogeneous Gaussian approximation to the Poisson statistics. The question then becomes whether or not the improvements in accuracy (if any) from using the Poisson model rather than the Gaussian approximation are significant enough to merit the additional computation. To investigate the accuracies of these algorithms, we are developing fundamental performance limits, described next.

Fundamental performance limits

Although it is widely known that all imaging systems and reconstruction methods have a tradeoff between resolution and noise, until recently there were no methods for specifying quantitatively lower limits on the noise at a given resolution. In collaboration with colleagues in Electrical Engineering, we have developed a method for imaging system and algorithm analysis based on an extension of the Cramer-Rao lower bound. This technique allows one to specify absolute lower limits (for a given PET system) on the achievable trade-off between bias and variance (i.e. resolution and noise). (Hero and Fessler, 1994b; Usman et al, 1994a; 1994b; 1994c)

With this method we can compute a bias-variance lower bound curve, and then compare the empirically determined performance of the PWLS and SAGE algorithms to this lower bound. The closer the bias-variance performance of the iterative algorithms is to the bound, then the closer to optimal their performance is. Preliminary results for SPECT imaging (Usman et al, 1994b;1994c) indicate that over a wide range of resolutions PWLS and SAGE algorithms have comparable performance that is within about 10 percent of the optimal (minimal) variance. As we refine this analysis method, we will perform more systematic comparisons between the performance of iterative and non-iterative reconstruction algorithms and the lower bounds.

Transmission tomography

In 3D PET one still performs 2D transmission scans, so one must first reconstruct an attenuation volume and then reproject to compute all of the required attenuation correction factors. We have also been developing iterative algorithms for reconstructing these attenuation maps with the goal of reducing the noise component due to attenuation correction and/or reducing transmission scan time. Previously we had proposed to use the PWLS algorithm for reconstructing the attenuation maps. However, we have found recently that, due to the low count rates in transmission scans coupled with the nonlinear logarithmic transform for transmission tomography, the PWLS method can have a systematic 5 to 10 percent underestimation of the attenuation coefficients. In contrast, the conventional FBP method has a systematic 5 to 10 percent overestimation, whereas a penalized maximum likelihood method is essentially unbiased. We confirmed these empirical findings with a new analysis of the bias (Fessler, 1994c). These findings led us to develop new algorithms for transmission tomography based on a penalized maximum likelihood objective function rather than the weighted least squares objective. In collaboration with Ken Lange, the developer of the transmission EM algorithm, we have investigated several parallelizable algorithms that converge significantly faster than the original EM algorithm (Lange and Fessler, 1994). We have also developed an even faster algorithm based on a hybrid Poisson/polynomial objective function (Fessler, 1994c). In this approach, we approximate the log-likelihood of the high-count detector measurements with a quadratic polynomial, the medium-count measurements with a cubic polynomial, but retain the original log-likelihood term for the low-count detector measurements. This approach allows us to capture the statistical advantages (i.e. unbiasedness) of the Poisson likelihood based approach, while requiring only slightly more computation time than the weighted least squares, since the fraction of low-count detectors is relatively small. Currently this hybrid algorithm is the fastest likelihood-based method we know of for transmission tomography.

We have also implemented the first version of our soft segmentation method using mixture models. Preliminary results show that this method is more accurate than the conventional hard segmentation approach (Fessler, 1994d).

Future work

The iterative algorithms described above have been implemented using a simple quadratic penalty function. This penalty function yields resolution characteristics comparable to that of FBP (but with reduced noise). It has long been the ultimate goal of statistical reconstruction methods to attempt to achieve significant improvements in both resolution and noise by using more sophisticated non-quadratic penalty functions. C. Bouman and K. Sauer have recently developed a non-quadratic penalty function that is self-similar and strictly convex. The penalty function has an edge-preserving property which should be particularly useful for reconstructing attenuation maps since those maps are piecewise smooth functions. We will compare this new penalty with the "soft segmentation" method for transmission reconstruction.

We expect further improvements in convergence rates can be achieved for emission reconstruction by adopting a hybrid Poisson/polynomial approach similar to that we have developed for transmission reconstruction. Nevertheless, we believe the development of the algorithms has reached a certain level of maturity and over the next year will begin more systematic evaluations using phantom data. Particularly important will be refining the PET system model to account for the circular geometry and the spatially variant resolution.

Optimization of Tracer Kinetic Modeling and CBF Activation Studies (Dr. Koeppe)

During the past project period in this subproject (2C) we have worked in two areas: 1) development and optimization of kinetic modeling configurations for two radiotracers, [^{11}C]raclopride and [^{11}C]dihydrotetrabenazine (DTBZ) and 2) the development of a method to enhance signal-to-noise in paired PET CBF activation studies.

Tracer Kinetic Modeling

Initial human PET studies have been performed and analyzed with several different kinetic model formulations to determine the optimal model configurations and data analysis strategies for two neurotransmitter/receptor ligands, [^{11}C]raclopride ([^{11}C]RAC), a dopamine D2 ligand which has already been used at several other PET facilities, and a completely novel ligand developed by our radiochemistry group, [^{11}C]dihydrotetrabenazine ([^{11}C]DTBZ), a marker for monoamine nerve terminal density.

[^{11}C]RAC studies have typically been performed with bolus injection followed by a single scan fairly late after injection (in the range from 30-90 min) when it is assumed that the tracer is at equilibrium. We have undertaken studies to compare a true equilibrium measurement (using a continuous infusion of tracer) to more accurately measure the steady-state condition and also have acquired bolus injection studies and performed kinetic analysis applying both 2- and 3-compartment models. For raclopride studies we used a 90 min acquisition protocol as follows: 2 x 30 sec; 4 x 1 min; 2 x 2.5 min; 2 x 5 min; and 7 x 10 min for a total of 17 scan frames. Arterial blood was sampled, separated in plasma and red cells, the plasma counted and metabolite corrections were performed by liquid chromatographic techniques to determine the authentic arterial plasma input function required for kinetic modeling. Six bolus infusion studies in young normal volunteers have been acquired and subsequently analyzed with both a 2-compartment pixel-by-pixel estimation of BBB transport (K_1) and ligand DV and a 3-compartment VOI analysis, estimating CBV, K_1 , k_2 , k_3 , and k_4 , where k_3/k_4 , (which has proven to be more stable than the estimates of either k_3 or k_4 alone) provides an estimate of B_{max}/K_D . For the pixel-by-pixel analysis, subtracting the value of DV in the cerebellum from DV in other regions provides a correction for the free + non-specific binding component of the total distribution volume in the same manner as a reference region is used in the equilibrium approach, thus yielding regional estimates of the specifically bound distribution volume (B_{max}/K_D). Six continuous infusion studies have also been performed. From this data, an equilibrium estimation of DV is made by taking the ratio of the tissue concentration to the metabolite corrected arterial plasma concentration at a late time when steady-state has been achieved (40-90 min in our studies). Both 2- and 3-compartment kinetic analysis were also performed on this data. Preliminary results indicate that the 2-compartment and equilibrium estimations of DV yield nearly identical values. When the free + non-specific distribution volume in the cerebellum (DV_{cb}) is subtracted from DV, these two methods are also in excellent agreement with binding estimates, k_3/k_4 ($=B_{\text{max}}/K_D$), from the 3-compartment kinetic analysis. Comparisons between kinetic analysis derived from bolus injection studies compared to continuous infusions studies also resulted in very similar estimates of DV, however, the continuous infusion studies yielded considerably noisier estimates of the BBB transport parameter, K_1 . Parts of these results have been reported (Minoshima et al, 1994f).

[^{11}C]DTBZ have been initiated in the past 4 months. We have acquired dynamic data on a total of 7 young normal volunteers. 15 scan frames were acquired over a 1 hr scan duration as follows: 4 scans x 30 s; 3 x 1 min; 2 x 2.5 min, 2 x 5 min; and 4 x 10 min. Blood sampling was again performed and metabolite corrections calculated to provide the arterial input function of authentic radiotracer. All studies to date have been performed using bolus administrations of tracer, however, we do plan to test and compare an equilibrium analysis using a continuous administration protocol, as has been accomplished with [^{11}C]RAC. Also, as was done with [^{11}C]RAC, both 2- and 3-compartment models have been applied for kinetic analysis. Initial results indicate that although [^{11}C]DTBZ has a high extraction and moderately rapid clearance rate

from the tissue (indicating rapidly reversible binding), a three compartment analysis yielding an estimate of k_3/k_4 improves the goodness-of-fit (as determined by an F-test for inclusion of additional model parameters) relative to a simple two compartment estimate of DV.

CBF Activation Studies

A limitation in the ability to detect small CBF changes with PET is the signal-to-noise (S/N) level. During the past year, we have explored one method of improving S/N which involves switching between "activation" and "control" conditions within scans rather than merely between scans. Thus rather than performing a purely "activation" scan and a purely "control" scan, then subtracting the two to discern differences between the two states, we perform a scan which begins with the subject performing the "activation" task and then switching to the "control" task at the time when activity in the brain reaches a maximum. Likewise, the other scan begins with the subject performing the "control" task, with the subject switching to the "activation" task when activity in the brain reaches a maximum.

Assuming that the "activation" state has higher flow than the "control" state for a particular region-of-interest, the theory is as follows. When looking for differences between the "activation" and "control" states, the signal will be proportional to the difference between the total number of coincidence events detected in the two scans, while the noise will be proportional to the total number of events detected. During the initial uptake of tracer, higher flow causes more rapid uptake of the tracer. Thus, during the uptake phase of the study, which is defined to be the time from injection to the peak activity in the brain (typically 30-40 sec after arrival of activity in the brain), the total detected counts in the scan will be higher for the "activation" task than the "control" task. However, during the washout phase of the scan, defined to be after the peak activity in the brain, higher flow will cause more rapid clearance of tracer, and thus the total number of detected counts in the scan during the washout phase will be lower for the "activation" condition. Therefore, to maximize the difference between two scans, one scan should have the "activation" task performed during uptake and the "control" task during washout, maximizing counts in the particular region, while the other scan should have the "control" task performed during uptake and the "activation" task during washout, minimizing counts in the particular region.

Two separate studies were performed on a total 16 young normal volunteers (8 per study), with each volunteer receiving 8 injections of 50 mCi [O-15]water; 2 replications of 4 different task conditions (described below). One study compared an object naming task (animals) with a size discrimination task (of irregular polygons). The second study involved two tasks, one requiring memory, one not requiring memory. For each study, the 4 task conditions were as follows: two conditions were the activation task alone [1] and the control task alone [2]. The other two conditions are the activation task switching to the control task [3] and the control task switching to the activation task [4]. The primary analysis was to determine whether areas of activation were of a greater magnitude and significant level for the "activation switching to control" scan minus the "control switching to activation" pair ([3]-[4]) than the straight "activation" minus the straight "control" pair ([1]-[2]). Results indicate that for both object naming-size discrimination and the memory-non-memory studies, the majority of the regions activated were more significantly activated in the [3]-[4] subtraction than the [1]-[2] subtraction. (Koepp et al, 1994b). For these studies we have concluded that S/N enhancements can be obtained by switching "activation" and "control" tasks during the PET scans even in cognitive testing where levels of activation are much less than those obtained with sensory or motor tasks.

Future Plans

We will be acquiring the new Siemens ACS-II package for performing and reconstructing 3-D data sets in the fall of this year. The majority of the plans for the coming year will center around optimizing data acquisition and analysis strategies for using 3-D PET both with tracer kinetic modeling studies of neuroreceptor/neurotransmitter ligands and with PET CBF activation studies.

Methodology for Analysis of Individual PET Image Data (Dr. Minoshima)

To improve accuracy in structural identification and data analyses of PET image sets, we have been investigating brain image standardization techniques for the past few years. Previously, we reported fully automated methods for detection of brain mid-sagittal plane and the intercommissural line, which were supported in part by the Department of Energy. These methods have been used as a routine image processing in our PET laboratories. In this year, we have investigated further linear and non-linear deformation of PET functional brain images which enables reliable between-group comparisons of PET image sets on a pixel-by-pixel basis (Minoshima et al. 1994a). This method detects multiple surface and subcortical landmarks on an individual PET image set and deforms the brain image to a uniform shape of the standard stereotactic atlas brain in an automatic fashion. The method has been implemented in an automated data analysis package for [O-15]water activation studies (Minoshima et al. 1994b). Using this technique, we demonstrated multiple areas of statistically significant cerebral activation during noxious heat stimulation (Casey et al. 1994, Minoshima et al. 1994c). We also constructed a PET stereotactic atlas of the human brain as a aid for visual interpretation of functional brain images in clinical settings (Minoshima et al. 1994d).

We are currently investigating objective image analysis methods for an individual brain PET image set in the standard stereotactic coordinate system, as a part of our proposal. Differences of individual image analyses in comparison to between-group analyses include presence of a relatively high noise level on a single PET image set and individual's anatomic variations in the standard stereotactic coordinate system. We estimated approximate locations of individuals' primary sensorimotor cortex in the stereotactic coordinate system in normal controls as well as in patients with Alzheimer's disease. We found accurate mapping of averaged locations of the sensorimotor cortex in both groups, but there were small but present individuals' variations which could not be removed entirely by existing stereotactic approaches (Ishihara et al. 1994). To take such small anatomic variations into account and to increase sensitivity of statistical analyses, we have developed a method for data extraction of regional functional information which is more robust to small anatomic variations and can reduce the amount of data on a PET image set effectively while preserving accuracy in anatomic localization. The method extracts metabolic information of lateral and medial brain structures using predetermined stereotactic surface pixels and iterative search for the location of the sensorimotor cortex. Pixel-by-pixel statistical analyses can be applied to this data format that has approximately 13% volume of an original image set. Furthermore, the extracted data can be viewed in stereotactic three-dimensional surface views, which greatly facilitates visual inspection. We used this technique to identify glucose metabolic abnormalities in patients with Alzheimer's disease (Minoshima et al. 1994e). In this analysis, regional cerebral metabolic values were extracted by the proposed method, and a database of normal glucose metabolism was constructed. An individual patient of Alzheimer's disease was compared to the database on a pixel-by-pixel basis in the extracted data format, resulting in an individual's Z-score map. By applying a statistical threshold to this map, we could identify 95% of patients with Alzheimer's disease, including early cases, without causing any false positives in the normal control group.

Future work

This technique facilitates objective analysis of an individual image set combined with a normal database or control data sets and will be investigated further for [O-15]water activation studies and other types of PET imaging. Methods for statistical analyses in the new data format will be addressed further. Quantitative accuracy of the proposed method will be investigated and will be compared with conventional region-of-interest analysis. Since the method has advantages for visual inspection of functional brain images, performance of such inspections will be compared between conventional slice presentation and 3D stereotactic surface presentation. The method will be combined with 3D PET imaging techniques.

Publications:

Published Papers/Papers in press

- Casey KL, Minoshima S, Berger KL, Koeppe RA, Morrow TJ, Frey KA. Positron emission tomographic analysis of cerebral structures activated specifically by repetitive noxious heat stimuli. *J Neurophysiol* 1994;71:802-807
- Fessler JA, Penalized weighted least-squares images reconstruction for positron emission tomography tomography, *IEEE Trans Med Imaging*, 1994a; 13(2):290-300.
- Ficaro EP, Fessler JA, Rogers WL, Schwaiger M: Comparison of AM-241 and TC-99m as transmission sources for the attenuation correction of Tl-201 SPECT imaging of the heart. *J Nucl Med*, 1994; 35:652-663.
- Koeppe RA, Frey KA, Mulholland GK, Kilbourn MR, Buck FL, Lee, KS, Kuhl DE: [¹¹C]Tropanyl benzilate binding to muscarinic cholinergic receptors: Methodology and kinetic modeling alternatives. *J Cereb Blood Flow Metab*, 1994a; 14:85-99.
- Kuhl DE, Koeppe RA, Fessler JA, Minoshima S, Ackermann RJ, Carey JE, Gildersleeve DL, Frey KA, Wieland DM: In vivo mapping of cholinergic neurons in the human brain using SPECT and IBVM. *J Nucl Med*, 1994; 35:405-410.
- Minoshima S, Koeppe RA, Frey KA, Ishihara M, Kuhl DE. Stereotactic PET atlas of the human brain: aid for visual interpretation of functional brain images. *J Nucl Med*, 1994d; 35:949-954.

Papers Accepted for Publication

- Fessler JA, Hero AO: Space-Alternating Generalized Expectation Maximization Algorithm. *IEEE Trans Signal Proc*, Oct. 1994a (in press)
- Hero AO, Fessler JA: Convergence in norm for alternating expectation-maximization (EM)-type algorithms. *Statistica Sinica*, 1994a (in press)
- Hero AO, Fessler JA: A recursive algorithm for computing CR-type bounds on estimator covariance., *IEEE Trans Info Theory*, 1994b (in press)
- Minoshima S, Koeppe RA, Frey KA, Kuhl DE. Anatomical standardization: linear scaling and nonlinear warping of functional brain images. *J Nucl Med* 1994a (in press)
- Minoshima S, Koeppe RA, Kuhl DE, Arimizu N. Integrated and automated data analysis for neuronal activation studies using positron emission tomography: methodology and applications. *Jpn J Nucl Med* 1994b (in press)

Papers Submitted for Publication

- Fessler JA, Hero AO: Hybrid Poisson/Polynomial Objective Functions for Tomographic Image Reconstruction from Transmission Scans. *IEEE Trans Image Proc*, 1994c (in review)
- Fessler JA, Hero AO: Suboptimality of the Truncated SVD for Ill-Conditioned Inverse Problems. *IEEE Trans Image Proc*, 1994b (in review)

- Fessler JA: Penalized Maximum-Likelihood Image Reconstruction Using Space-Alternating Generalized EM Algorithms. *IEEE Trans Image Proc*, 1994b (in review)
- Ishihara M, Minoshima S, Cho K, Koeppe RA, Kuhl DE. Partial validation for bicommissural stereotaxy in Alzheimer's disease: localization of the primary sensorimotor cortex. *Annals of Nuclear Medicine* 1994 (in review)
- Lange K, Fessler JA: Globally convergent algorithms for maximum a posteriori transmission tomography. Submitted *IEEE Trans Image Proc*, 1994 (in review)
- Minoshima S, Frey KA, Koeppe RA, Foster NL, Kuhl DE: Cerebral glucose metabolic pattern in Alzheimer's disease: a new diagnostic index and image presentation of [^{18}F]FDG. *J Nucl Med* 1994e (in review)
- Usman M, Hero AO, Fessler JA.: Bias-variance trade-off analysis using the biased CR-bound for a simple SPECT system. Submitted to *IEEE Trans Signal Proc*, 1994a (in review)
- Usman M, Hero AO, Fessler JA: Application of the uniform CR bound for performance evaluation and system design. Submitted to *IEEE Trans Med Proc*, 1994b (in review)
- Usman M, Hero AO, Fessler JA: Recursive algorithms for computing the Cramer-Rao bound. Submitted to *IEEE Trans Signal Proc*, 1994c (in review)

Abstracts

- Fessler JA: A mixture-site model for edge-preserving image restoration. In *Proc IEEE Intl Conf on Image Processing*, 1994c (in press).
- Koeppe RA, Minoshima S, Buchtel HA, Botti LE, Henry TR: Enhanced detectability of CBF changes in PET [0-15] water activation studies of human cognition. *J Nucl Med*, 1994b; 35(5):138P.
- Minoshima S, Frey KA, Koeppe RA, Morrow TJ, Kuhl DE. Temporal modulation of cerebral involvement in pain perception revealed by [0-15]water PET in humans. *J Nucl Med*, 1994c; 35(5):33P.
- Minoshima S, Koeppe RA, Mukhopadhyay S, Jewett D, Kuhl DE, Kilbourn MR, Frey KA: Equilibrium measurement of [C-11]raclopride distribution volume in the brain using a continuous infusion technique. *J Nucl Med*, 1994f; 35(5):140P.

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