DOE/ER/60438--4

DE92 016969

NUCLEAR MEDICINE AND IMAGING RESEARCH
(Quantitative Studies in Radiopharmaceutical Science)

PROGRESS REPORT
FOR THE PERIOD JANUARY 1, 1992 THROUGH DECEMBER 31, 1992

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June, 1992

Prepared for
THE U.S. DEPARTMENT OF ENERGY
UNDER GRANT NO. DE-FG02-86ER60438

THE

FRANKLIN McLEAN MEMORIAL RESEARCH INSTITUTE

DEPARTMENT OF RADIOLOGY

PROGRAM OF

NUCLEAR MEDICINE AND QUANTITATIVE IMAGING RESEARCH

THE
UNIVERSITY OF CHICAGO

QUANTITATIVE STUDIES

IN

RADIOPHARMACEUTICAL SCIENCE

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GRANT NO. DE-FG02-86ER60438

NOTICE

Section I
Radiochemistry
(Jogeshwar Mukherjee, Ph.D., Section Leader)

We have reported development and use of the benzamide neuroleptic, [^{18}F]FPMB in recent papers. In attempts to improve brain uptake while maintaining high affinity for the D-2 receptor-sites, we report investigation of five new analogs of [^{18}F]FPMB which result from modifications of the ethyl group at the pyrrolidine nitrogen in [^{18}F]FPMB.

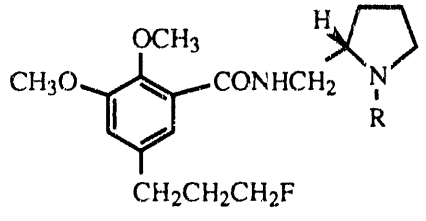
A. Fluorinated Substituted Benzamides as Dopamine D-2 Receptor Tracers:

The first compound that we developed was (S)-N-[1-ethyl-2-pyrrolidinyl)methyl]-5-(2-[F-18]fluoroethyl)-2-methoxybenzamide. We have reported synthesis and radiosynthesis of this compound in a recent paper. Synthesis of FPMB and radiolabeled [F-18]FPMB has been reported by us recently. We have now prepared five additional derivatives by modifying the ethyl group at the pyrrolidine nitrogen. Alkylation of (S)-pyrrolinamide was carried out with various alkyl halides in THF. The amide was then subsequently reduced with diisobutylaluminum hydride (DIBAL) to provide the respective aminomethyl-derivatives. These were then coupled with the substituted acid fluoride to provide the various derivatives. As discussed in Significance, for sulpiride, it has been reported that a n-propyl group instead of an ethyl group increases the affinity four-fold whereas an allyl group at this position shows a fifteen-fold increase in affinity.

Binding affinities for the dopamine D-2 receptor were determined on rat and human striata. Affinities of unlabeled compound were determined by competition at rat striatal dopamine D-2 receptor binding sites labeled with [^{125}I]epidepride. Specific binding was determined by 10 μM (*S*)-sulpiride. Aliquots of tissue were incubated for 4 hours at 27°C in duplicate with 0.2 nM [^{125}I]epidepride and increasing concentrations of unlabeled compound (ranging from 0.01 nM to 10 mM). Final assay volume was 1.0 mL. Competition isotherms were analyzed by LIGAND to provide IC_{50} of the unlabeled compound.

We have measured binding affinities of the various N-alkylated derivatives and their apparent lipophilicites log kw, at pH 7.5. These are shown in Figure-2. Increasing the lipophilicity, increased the affinity of all the derivatives except the iso-propyl. We have not tested the iso-butyl derivative yet. Allyl group showed the largest increase in affinity (from 2,44 to 0.28 nM, almost 10-fold). A plot of affinity, pC (-log nM) and apparent lipophilicity, log kw (Figure-3), shows a parabolic relationship with an optimal lipophilicity of approximately, log kw of 2.1.

Figure-1: Structural Studies in Benzamides.



S.No.	R	log kw	IC_{50}, nM
1.	CH_2CH_3	1.64	2.44
2.	$CH_2CH_2CH_3$	1.90	0.56
3.	$CH(CH_3)_2$	1.96	33.8
4.	$CH_2CH{=}CH_2$	2.43	0.28
5.	$CH_2CH_2CH_2CH_3$	2.28	0.74
6.	$CH_2CH(CH_3)_2$	2.52	25.8

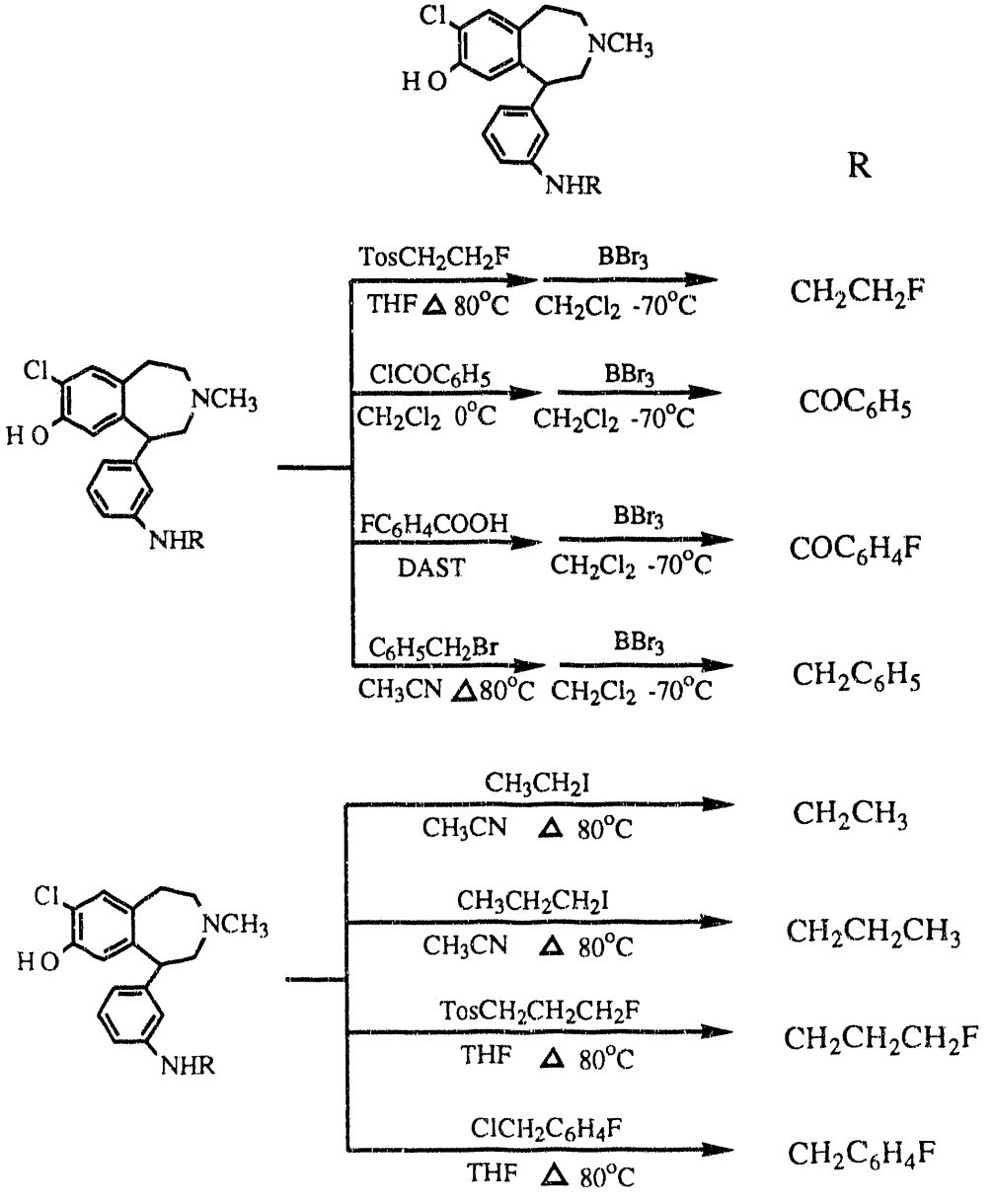
B. Fluorinated Substituted Benzazepines as Dopamine D-1 Receptor Tracers:

Substituted benzazepines have been prepared as specific dopamine D-1 receptor antagonists. One of the specific ligands, (R)-(+)-8-chloro-2,3,4,5,-tetrahydro-3-methyl-5-phenyl-

1H-3-benzazepine-7-ol (SCH 23390) has been shown to possess high affinity for the D-1 receptor sites. The most likely position for radiolabeling with fluoroalkyl or fluoroaryl groups would be the aromatic ring. To this effect, we have made fluoroalkyl and fluoroaryl derivatives of the amino derivative, SCH 38548. The binding affinity of SCH 38548 (K_D= 1.5 nM for the racemic mixture) is not significantly different from SCH 23390 (K_D=0.53 nM for the pure R-isomer).

Synthesis of SCH 38548 was carried out by modifying the reported procedure. Derivatives of SCH 38548 have been prepared as outlined in Figure-2. Two approaches were used: a) O-methylated SCH 38548 was first appropriately derivatized, which was then followed by deprotection of the O-methyl group with boron tribromide, and b) SCH 38548 was directly used to derivatize. The second approach involved purifying the product from side-products resulting from O-alkylations. All products were purified by preparative thin layer chromatography and characterized by mass spectral analysis and nuclear magnetic resonance spectroscopy.

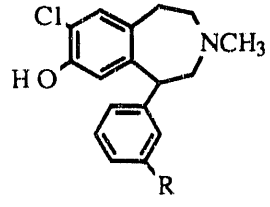
Figure-2: Synthesis of Various Benzazepine Derivatives



Receptor affinities of all the compounds were measured using rat brain striatal tissue. Affinities were measured for dopamine D-1 receptor sites using [H-3]SCH 23390, for dopamine D-2 receptor sites using [H-3]spiperone along with ketanserin to block serotonin receptor binding of [H-3]spiperone and for serotonin 5HT-2 receptor sites using [H-3]spiperone along with haloperidol to block dopamine D-2 receptor binding of [H-3]spiperone.

Results obtained on all the derivatives are very encouraging. Shown in Figure-3 are the IC50 values (nM) for the fluorinated derivatives at the three receptor sites. All compounds showed high affinity for the dopamine D-1 receptors and poor affinities for the D-2 and serotonin 5HT-2 receptors. Selectivity ratios in favor of the D-1 receptors were very high compared to that obtained for SCH 23390 which shows significant affinity for the serotonin 5HT-2 receptor sites as well. This indicates that all the four fluorinated derivatives are potential selective D-1 receptor radiotracers when radilabeled with fluorine-18. Of the four derivatives the p-fluorobenzoyl derivative shows the highest affinity for the D-1 receptor, almost similar to that observed for the parent compound, SCH 38548.

Figure-3: Fluorinated derivatives of SCH 38548



		Affinity, IC50, nM			Selectivity	
	R	D-1	D-2	5HT-2	D-2/D-1	5HT-2/D-1
1	H	0.4±0.1*	359*	13.1*	896*	33*
2	NH_2	0.53±0.46	3100	2200	5849	4150
3	$NH(CH_2)_2F$	4.02±2.10	$2.5x10^4$	10^5	1243	$3.5x10^4$
4	$NH(CH_2)_3F$	4.80±3.60	10^6	10^6	$2.45x10^4$	$22.9x10^4$
5	$NHCH_2C_6H_4F$	1.53±0.81	$1.6x10^4$	10^6	$1.02x10^4$	$65.4x10^4$
6	$NHCOC_6H_4F$	0.55±0.33	270	10^6	490	$181x10^4$

* Ki's, nM taken from Chipkin et al, J. Pharm. Exp. Ther., 247:1093 (1988). All other values were measured by us and are reported as IC50, nM.

We have carried out radiosynthesis of *N*-2-[^{18}F]fluoroethyl, *N*-3-[^{18}F]fluoropropyl and *N*-p-[^{18}F]fluorobenzoyl derivatives. [^{18}F]fluoroethyl bromide and [^{18}F]fluoropropyl iodide were produced by reacting nca [^{18}F]fluoride/kryptofix/K_2CO_3 with dibromoethane and diiodopropane respectively, in CH_3CN at 75°C. [^{18}F]fluoroalkylation was carried out in dimethylformamide at 110°C. *N*-[^{18}F]fluoroalkylated derivatives were separated using HPLC in 12-15% yields in specific activities of 1.4 Ci/μmol. For *N*-p-[^{18}F]fluorobenzoylation of SCH 38548 (Figure-4), p-[^{18}F]fluorobenzoyl fluoride was produced from p-nitro-benzaldehyde in three steps (nucleophilic [^{18}F]fluoride rxn, oxidation by Jones reagent followed by treatment with DAST). *N*-p-[^{18}F]fluorobenzoyl derivative was obtained in 6-10% yields in specific activities of 1.5 Ci/μmol.

Preliminary rat biodistribution studies of [^{18}F]fluorobenzoyl derivative have been carried out. Brain to blood ratios of the tracer increased with time reaching about 18 three hours post-injection. Bone uptake was minimal as evidenced by a marginal increase in bone to blood ratios (approximately 3 three hours post-injection). Figure-5 shows cortex to cerebllum ratios which remained constant whereas striata to cerebellum ratios increased to approximately 8 three hours post-injection. Specific uptake of the tracer in the striata was blocked by coadministration of SCH 23390. Also, specific uptake in the striata was displaceable with SCH 23390. These results indicate the potential usefulness of this compound as a PET radiotracer.

Figure-4: ^{18}F-Fluorobenzoylation of SCH 38548

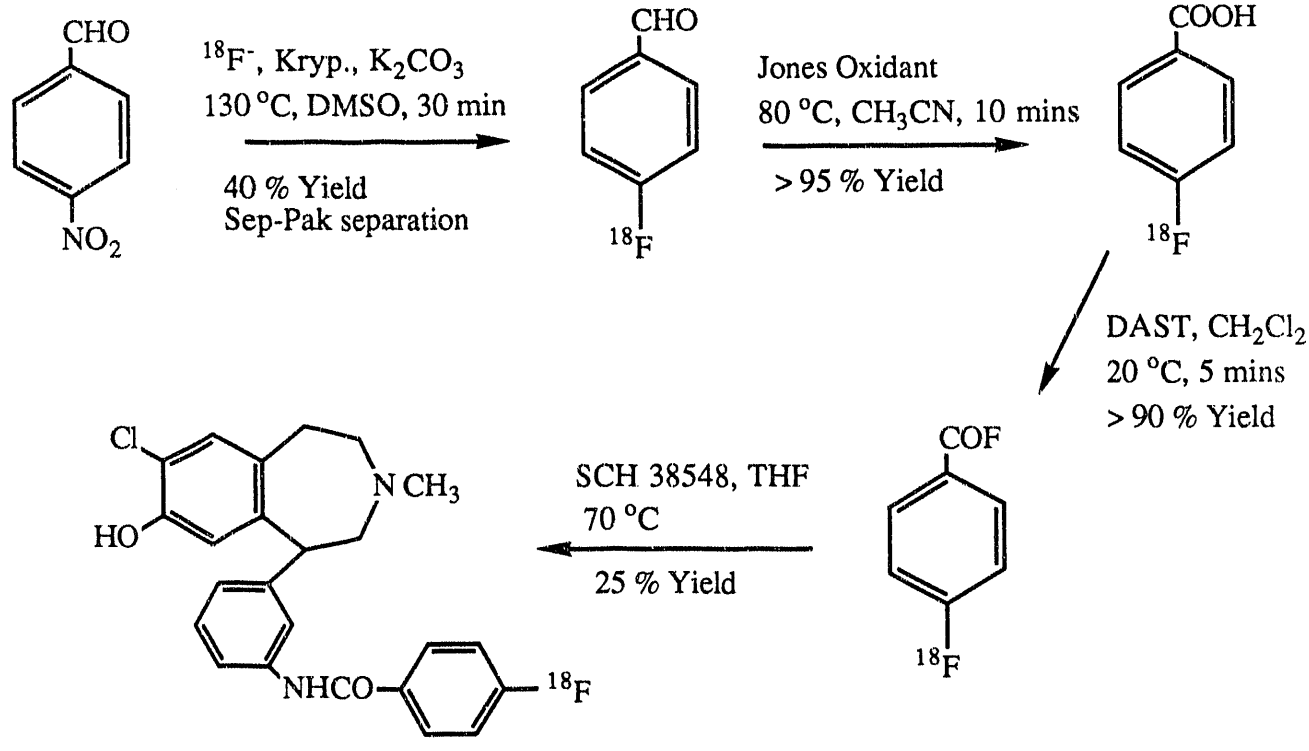


Figure-5: Biodistribution of N-^{18}F-FluorobenzoylSCH 38548 in Rats

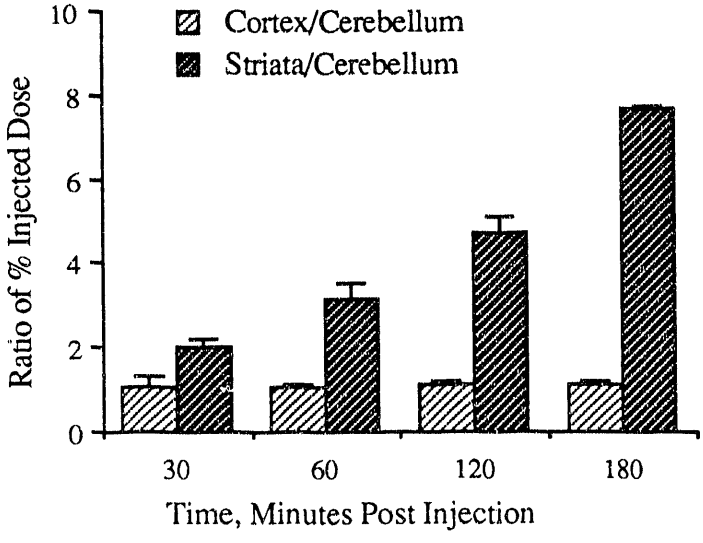
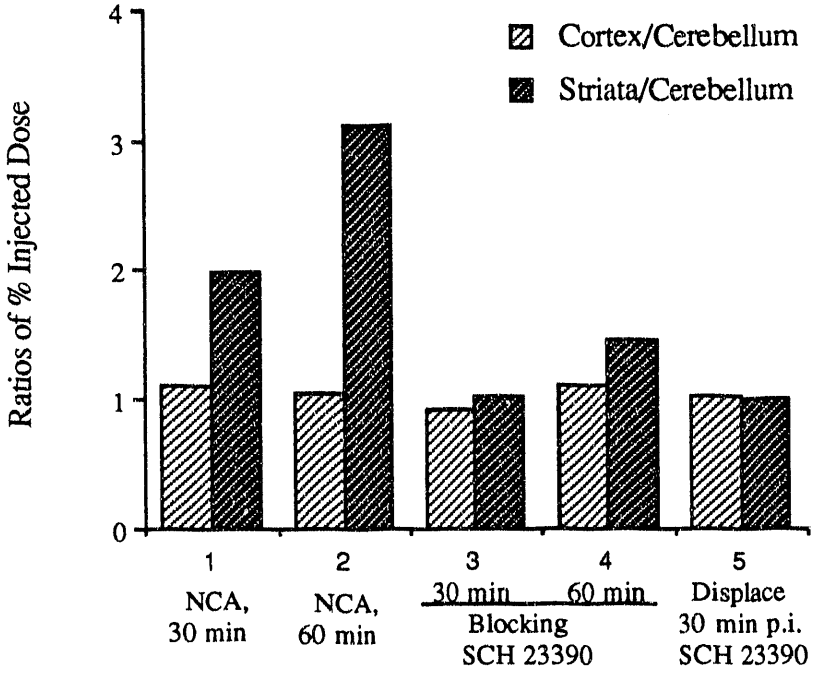


Figure-6: Specific Uptake of N-^{18}F-FluorobenzoylSCH 38548 in Rat Brain



C. ^{18}F-Fluoxetine as a Serotonin Reuptake-Site Tracer:

Fluoxetine (Prozac) is a clinically used potent antidepressent. The therapeutic effect of fluoxetine and its major metabolite, norfluoxetine depends on their ability to selectively inhibit presynaptic uptake of serotonin. Radiolabeled fluoxetine may therefore be a potential tracer for the serotonin reuptake-sites. Carbon-11 labeled fluoxetine has been prepared, but does not seem to hold promise as an *in vivo* tracer. This may be due to the fact that fluoxetine is rapidly demethylated to norfluoxetine resulting in a loss of the radiolabel. Additionally, norfluoxetine also binds quite strongly at the receptor site, thus possibly competing for the receptor-sites with any of the remaining radiolabeled fluoxetine. We have therefore considered radiolabeling fluoxetine with fluorine-18 by replacing one of the native fluorines in the molecule. Radiosynthesis of [F-18]fluoxetine using related methods have recently been reported by Hammadi and Crouzel.

For purposes of incorporating fluorine-18 into the molecule, the precursor, a-bromo-a,a-difluoro-p-nitrotoluene was prepared using modifications of reported methods. Difluorination of p-nitrobenzaldehyde was carried out using DAST to provide a,a-difluoro-p-nitrotoluene. Bromination, using bromine and benzoyl peroxide as a catalyst, provided a-bromo-a,a-difluoro-p-nitrotoluene in approximately 30% yield. Radiolabeling was carried out by nucleophilic displacement of the bromide with [F-18]fluoride, using Kryptofix and potassium carbonate in anhydrous dimethylsulfoxide. The reaction was carried out at various temperatures (90 to 160) without any noticeable change in radiochemical yield. However, at higher temperatures there was greater decomposition of the starting material, and in some instances it completly disappeared. We plan to investigate the effect of temperature on the specific activity. Average radiochemical yields of 10-15% of a-^{18}F-fluoro-a,a-difluoro-p-nitrotoluene have been obtained in a reaction time of 20 minutes. (*S*)-(-)-3-(methylamino)-1-phenyl-1-propanol was converted to a lithium salt and taken up in anhydrous DMSO. Into this solution, radiolabeled a-^{18}F-fluoro-a,a-difluoro-p-nitrotoluene was trapped using a stream of nitrogen from the first reaction flask. The coupling reaction was carried out at 95 oC for 90 minutes to provide small amounts of [F-18]fluoxetine. Purification of

[F-18]fluoxetine was carried out on reverse-phase HPLC using a acetonitrile-0.001M phosphoric acid gradient. Rat biodistribution studies are planned.

Manuscripts/Presentations from Preliminary Work:

1. Mukherjee J, Z-Y. Yang, B.D. Perry and M. Cooper: Fluorine-18 derivatives of 7-chloro-8-hydroxy-3-methyl-1-(3'-aminophenyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (SCH 38548): Selective and high affinity fluorinated radioligands for dopamine D-1 receptors. Presented at the*IXth International Symposium on Radiopharmaceutical Chemistry,* Paris, April 6-10, 1992.

2. Fang Y-B, Mukherjee J and M. Cooper: Alternate Syntheses of (S)-N-[(1-Ethyl-2-Pyrrolidinyl)Methyl]-3-[^{125}I]Iodo-5,6-Dimethoxysalicylamide (Ioxipride) and (S)-N-[(1-Ethyl-2-Pyrrolidinyl)Methyl]-5-[^{125}I]Iodo-2,3-Dimethoxybenzamide (Epidepride): High Affinity and Selective Dopamine D-2 Receptor Radioligands. Presented at the*IXth International Symposium on Radiopharmaceutical Chemistry,* Paris, April 6-10, 1992.

3. Mukherjee J, Z-Y. Yang, B.D. Perry and M. Cooper: [F-18]fluorinated derivatives of SCH 38548 as potential PET radiotracers for dopamine D-1 receptors. Presented at the*40th Annual Meeting of the Association of University Radiologists,* Chicago, Illinois, April 20-26, 1992.

4. Mukherjee J, Z-Y. Yang, B.D. Perry and M. Cooper: High affinity and selective [F-18]fluorinated derivatives of SCH 38548 as potential PET radiotracers for dopamine D-1 receptors. Presented at the*39th Annual Meeting of The Society of Nuclear Medicine*, Los Angeles, California, June 9-12, 1992.

5. Fang Y-B, Mukherjee J, Yang Z-Y. and M. Cooper: Alternate Syntheses of [^{125}I]-Ioxipride and [^{125}I]-Epidepride: High Affinity and Selective Dopamine D-2 Receptor Radioligands. Presented at the*39th Annual Meeting of The Society of Nuclear Medicine*, Los Angeles, California, June 9-12, 1992.

6. Mukherjee J, Z-Y. Yang and M. Cooper: Syntheses, Pharmacological and lipophilicity studies of improved analogs of the D-2 PET tracer, [F-18]FPMB. Presented at *The Sixth Symposium on the Application of Cyclotrons*, Turku, Finland, June 1-4, 1992.

7. Das MK, J. Mukherjee and M. Cooper: Radiosynthesis of [F-18]fluoxetine as a potential radiotracer for serotonin reuptake sites. Submitted to the *Third International Symposium on Radiohalogens*, Banff, Alberta, September 20-23, 1992.

SECTION II

Pharmacology and Cognition

(John T. Metz, Ph.D., Section Leader)

Our work during the previous year has been significantly affected by the fact that our cyclotron has been unavailable for PET studies. While that situation is being remedied, we have devoted our efforts to establishing background information and preparing for the next series of studies that will be conducted once the cyclotron is available. For convenience, our progress during the past year can be grouped under the two principal headings for this section.

Pharmacology

Our major accomplishment has been to obtain separate funding for most projects in this section (H. de Wit, P.I.). New developments in our image analysis group (image registration and subtraction, relation to MRI) are now complete and we expect to be able to re-examine some previously collected data to determine if there are subtle changes due to drugs that we missed in our first analyses. These methods, of course, will be available from the beginning in all future studies.

We have finished a study in which we examined the mood-altering effects of amphetamine in the same subjects tested in the PET environment and in a recreational drug-taking environment. Briefly, consistent with our between-subject observations (3) we found that subjective effects are attenuated in the PET setting. We also found that the PET environment itself consistently alters subjects' mood (e.g., increasing fatigue, decreasing friendliness), even without drug administration (2; 4). These effects may interact with the pharmacological effects of drugs on a particular subject's mood.

We have completed two preliminary studies on the effects of serotonergic agents on cerebral metabolism. A pilot time course study was conducted to determine the effects of fenfluramine (FEN), an agent that releases serotonin and inhibits its reuptake, on cerebral metabolic rate of glucose (CMRglu). Four normal male subjects (ages 31-35) were each studied on 4 separate days at least 2 weeks apart. Six to 7.5m Ci of [18F]-2-deoxyglucose (FDG) was injected after placebo or 2, 3, or 4 hours after oral administration of 60 mg d,l-FEN. The order of drug administration was varied and double-blind. Subjects were studied while performing a visual monitoring task during acquisition of PET data with PETT VI. Compared to placebo, FEN did not have any significant group mean effects on regional or global CMRglu at any time point. However, individual subjects were consistent in their responses to FEN; those who had low placebo global CMRglu increased in response to FEN with a maximum increase at 3 hours; those who had high placebo CMRglu decreased in response to FEN with a maximum decrease at 3 hours. The average absolute percent change from placebo in global CMRglu was 12%, 18%, and 4.3% at 2, 3, and 4 hours after FEN, respectively. This pilot study did not reveal significant mean effects of FEN on CMRglu, although individual responses were largest 3 hours after FEN (1). These findings suggest that pharmacological challenge studies with more selective and direct 5-HT agonists may reveal less heterogeneous responses of regional or global CMRglu.

The second study is the first phase of a larger study comparing cerebral metabolism in normal and autistic subjects. The hypotheses to be tested in this study are that cerebral metabolism will not differ between autistic and normal control subjects in a behaviorally controlled baseline (placebo) condition. However, after phamacological

challenge with a potent and selective serotonin reuptake inhibitor, fluoxetine, global cerebral metabolism of autistic subjects will differ from controls. We have now completed data collection on four normal subjects. Each subject participate in two PET sessions. All studies were double-blind. Subjects received either fluoxetine, 40 mg, or placebo 90 minutes before FDG injection. These data are now being analyzed. Additional subjects, including high functioning autistic patients, have been recruited and are scheduled to be tested in the fall.

Cognition

All computer software for PET/PET and PET/MRI correlations and manipulations are available and tested. Our image analysis group will be continuing over the next several years to upgrade these programs, usually in the direction of making them easier for temporary student workers and collaborators to use. These upgrades will also be essential to deal with the high volume of data which we are anticipating.

The behavioral tasks for future PET studies of cognition require special equipment. A special monitor which connects to a Macintosh IIci computer has been obtained and fitted to our existing frame for presenting the tasks to subjects positioned in the scanner. This monitor will permit rapid switching between computer input and VCR input. It will also provide touch-screen capabilities so that subject responding will be easier and more natural.

Paradigms for cognitive projects on vision, memory, and mood have been tested in the behavioral laboratories of our collaborators (Dr. Hugh Wilson, Dr. John Gabrieli, and Dr. Richard Davidson). Dr. Jaswinder Singh, a post-doctoral neuropsychologist with expertise and experience in the psychophysiology of memory, has been added to our staff. He is supervising retested of the behavioral tasks in the PET lab. The recent behavioral data are also being analyzed. In analyses of the memory/SRT behavioral paradigm, we confirmed that normal subjects clearly performed better than patients with Huntington's disease or cerebellar lesions. Most importantly, the normal subjects (and the patients with cerebellar lesions) showed a pattern of progressively lower reaction times as they were exposed to a motor learning task, then a return to the initial level when the control task was reintroduced. In contrast, the Huntington's patients did not show this pattern, confirming that the task may be mediated by regions of the basal ganglia.

Although future studies in cognition will utilize O-15 labeled water as the tracer, we have tested some of the methods in studies using FDG. Because of the much shorter time required for data acquisition, we expect that behavioral signals in O-15 rCBF studies will be even larger and more discrete (5). These studies have established the value of PET/MRI and PET/PET correlations prior to pixel-by pixel subtraction (6). They have also confirmed the merit of within-subject averaging of similar conditions, one of the key features of our strategy for improving signal detection and quantitation.

References:

1. Cook EH Jr, Metz J, Cooper M, Chou J-S, Leventhal B (1991): Fenfluaramine effects on cerebral glucose metabolism. American Psychiatric Association 144th Annual Meeting, New Orleans, LA.
2. de Wit H, Metz JT, Cooper M (1989): Effects of diazepam on mood and regional cerebral metabolism using PET. *American College of Neuropsychopharmacology Abstracts*220.
3. de Wit H, Metz JT, Cooper M (1991): Methodological issues in the use of PET to study drugs of abuse. NIAAA Workshop on Imaging in Alcohol Research, Wild Dunes, S.C.

4. de Wit H, Metz JT, Wagner N, Cooper MD (1990): Behavioral and subjective effects of ethanol: Relationship to cerebral metabolism using PET. *Alcoholism* 14:482-489.
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6. Pelizzari CA, Chen GTY, Spelbring DR, Weichselbaum RR. Chen C-T (1989): Accurate 3-dimensional registration of CT, PET and MR images of the brain. *J Comput Assist Tomogr* 13:20-26.

Section III
Quantitative Image Analysis
(Chin-Tu Chen, Ph.D., Section Leader)

III-1. Detection of Local Changes of Brain Function

Image Registration

We have developed a surface-fitting method for integration of images obtained by different modalities or acquired at various times (J2,J4,P2,P9,A1,A3). This technique is widely recognized as the method of choice for correlating structural/functional brain images from CT, MRI and PET/SPECT. This method has been employed for many applications using the concept of image fusion, including 3-D visualization (J6,P9,P11,P15,A11,A13,A15,A20), surgical planning and radiation therapy planning (P14,P15,A15), localization of internal brain structures (J23), improving quantitation of PET image data (P5,P18,P20,P25,P33,P34), and multi-modality image reconstruction (J26). The surface-fitting technique has also been improved to become more accurate, more widely applicable, and more user-friendly. A semi-automated prototype system (P21) that performs this image registration procedure without much user interaction has also been developed on SUN SPARC station with UNIX and Motif environment. A comparison study was performed to assess the merit of the surface-fitting method and a land-mark approach (P28). We have also modified the original surface-fitting technique, which was based on using the surface of the head, to handle the situation in which only two sets of emission images, thus the surfaces of the brain, are available for registration. This approach has been employed in studies involving detection of subtle brain signals under different experimental conditions, which require registration of multiple emission images because of shifts in subject's position between repeat scans (P34,P35,A35).

Image Interpolation

Based on an elastic dynamic interpolation technique for reconstruction of 3-D shape from a series of 2-D contours (J1,J5,P1,A2), we have developed an improved technique which employs the spline theory and a surface consistency approach to produce a more accurate and smoother 3-D surface (J7,J8,P10,A14). We have also developed an intensity interpolation scheme that is based on the same concept of the elastic model but extended to generate a collection of internal rims for intensity interpolation of internal pixels (J23,P8,P12,P16,P22,A14). In addition, we built a prototype of an automated system for performing the task of image interpolation for routine studies (J15).

Signal Detection in a Single Subject and Signal Averaging of Multiple Studies

We have performed a series of preliminary studies using FDG/PET method to localize changes in cerebral glucose metabolism as a response to visual and somatosensory stimulations (P33,P34,A35,A36). In these studies, we tested a normalization procedure in which only gray-matter regions were considered and the difference images were produced by subtracting the pair of images after both has been re-computed according to the statistical z-transformation for each pixel identified as in the gray-matter regions. We also incorporated the image registration procedure for compensation for possible shifts in subject position between two scans. The resulting different image showed marked indications of responses to visual and somatosensory stimulations. The anatomical locations of these cognitive/sensory signals were also identified by overlapping with the corresponding structural map provided by the spatially-correlated MR image. We also performed an additional study under somatosensory stimulation on one subject, thus allowing us to obtain a

second set of difference image. By averaging the two sets of difference images, it was evident that both the visual signals and somatosensory signals were enhanced. In addition, a neural network approach for motion analysis (J24,J25) and a computational model for deformation process (J26) are under pursuit as a basis for developing a warping technique for transforming brain images of different subjects to a standard brain model.

Alternative Methods for Image Reconstruction

Snyder and Politte at Washington University has demonstrated that the cognitive signals detected in PET difference images can be significantly enhanced if the PET images were reconstructed by the EM (expectation-maximization) algorithm based on the maximum likelihood model. We have demonstrated that the EM algorithm can enhance signals in radiographic images (J21, A20). Under other supports including our accompanying DOE grant on "Instrumentation and Quantitative Methods of Evaluation, we have also developed several maximum likelihood and Bayesian methods for image reconstruction and demonstrated their ability to improve image quality (see, for example, J11). We have initiated implementation of these approaches as alternative image reconstruction strategies for enhancing the signals under study in this research.

III-2. Intelligent Systems for the Analysis of Multi-dimensional Nuclear Medicine Image Data

Image Segmentation

We have investigated the utility of many signal-based boundary detection and image segmentation algorithms (P4,A7), especially in application to volume estimation using nuclear medicine data (A5), and concluded this type of approaches alone is not adequate for multi-modal image segmentation (P7). Instead, knowledge-based approaches seem to be more capable of performing this task (J2,,P13). We therefore developed a boundary detector based on the fuzzy logic approach and proved to be useful in handling low-quality image such as those acquired in ultrasound or nuclead medicine imaging (J12,J17,P12). We have developed an adaptive slit-and-merge image segmentation algorithm for the initial segmentation step in the expert vision system (J14). This is a region-based segmentation algorithm which combines the strength of characteristic feature analysis and hypothesis model to produce an initial segmentation. 3-D implementation and parallel computing have been considered as well (P29,P30,A22). We have also formulated the problem of image segmentation as a Constraint Satisfaction Problem (CSP) and developed a general framework of a Constraint Satisfaction Neural Network (CSNN) for solving the problem of image segmentation (J16,J19,P23,P26). This technique is computationally very efficient and has also been extended to problems of image understanding (J20). The CSNN technique and the slit-and-merge technique described above have been applied to CT. MR, and PET images for producing the initial segmented images to be used in the expert vision system for ROI identification.

Expert Vision System

We have employed the Dempster-Shafer (D-S) theory for integration of uncertain information about the brain anatomy, brain function, imaging devises, and expert's knowledge of interpreting brain function and images (J27,P24,P27,P31,P35). The D-S theory employed in this system incorporates the concept of compatible frames and multivariate belief functions. These two features form the core of the reasoning scheme in the expert vision system. This system is capable of using the reasoning process of a human expert to divide a set of CT, MR, and PET images into semantically meaningful entities.

Physiological Modeling

We have employed several techniques for regional quantitative measurements and physiological modeling in assessing new radiopharmaceuticals (J9,A16), estimating internal radiation absorbed dose (J13,J18,A8,A9), and applications in clinical studies (J10,PP3,P6,P17,A4,A6,A10,A12,). We have performed a preliminary investigation of the principal component analysis (PCA) and factor analysis (FA) methods using a computer-simulated dynamic series (P33,A22,A23). Preliminary investigation of these methods were first performed on a computer-simulated dynamic series. A mathematical phantom was constructed by defining two anatomic images with distinct time functions. Each image represents a theoretical organ having a distinct physiology which is characterized by its tirne function. The two organs contained a region of overlap, as is usually the case in reality. The first 2 principal components extracted from the PCA of the noise-free dynamic series account for essentially all of the dynamic variation, as indicated by the sum of their eigenvalues. The final factor analysis of this ideal dynamic series produced 2 factor images and associated time functions which were essentially identical to the original anatomic organs and physiologic time functions. The dynamic series was reconstructed using only the first 2 PCs to produce a new series with a drastically enhanced signal-to-noise ratio (SNR). The factor rotation of the 2 PCs adequately recovered the 2 original anatomic images and physiologic functions. These methods have been applied to dynamic renal studies routinely acquired using a 30 minute, dual-phase acquisition. A bolus injection of 12-15 mCi of Tc-99m DTPA is given to the patient and images are acquired on a gamma camera at a rapid frame rate of 1 second/frame for the first minute (60 images) followed by 15 seconds/frame for the remaining 29 minutes (116 images). The PCA of the early bolus phase resulted in a data reduction from 116 acquired images to 4 PC images and 4 corresponding time curves. The reconstruction of the dynamic series using only the first four components resulted in an SNR enhancement of greater than a factor of 10. After applying the general constraints, The factor rotation produced images and time functions which are consistent with the known anatomy and and expected hemodynamics. The factor analysis of the later images acquired from 1-30 minutes resulted in the generation of factor images representing the accepted plasma, exchange, and collection compartments. Their associated time factors demonstrated a direct correspondence to the dynamics predicted by the conventional 3 compartment model. The validity of these factors has been demonstrated by comparing the plasma time factor to the measured plasma curve obtained from rapid blood sampling. The regression analysis of the measured plasma sample data against the factor plasma curve resulted in a correlation coefficient of 0.988 (P33,A23).

Journal Papers:

Relevant Previous Publications

J1. Lin, W.-C., Liang, C.-C. and Chen, C.-T.: Dynamic elastic interpolation for 3-D medical image reconstruction from serial cross-sections. *IEEE Trans Med Imaging* **MI-7**:225-232, 1988.

J2. Levin, D.N., Pelizzari, C.A., Chen, G.T.Y., Chen, C.-T. and Cooper, M.D.: Retrospective geometric correlation of MR, CT, and PET images. *Radiology* **169**:817-823, 1988.

J3. Lin, W.-C., Weng, Y.-T. and Chen, C.-T.: Expert vision systems integrating image segmentation and recognition processes. *Eng Appl of Artificial Intelligence* **1**:230-249, 1988.

J4. Pelizzari, C.A., Chen, G.T.Y., Spelbring, D.R., Weichselbaum, R.R. and Chen, C.-T.: Accurate three-dimensional registration of CT, PET and MR images of the brain. *J Comput Assist Tomogr* **13**:20-26, 1989.

J5. Lin, W.-C., Liang, C.-C. and Chen, C.-T.: A computational model for process-grammar. *Artificial Intelligence* **38**:207-224, 1989.

J6. Levin, D.N., Hu, X., Tan, K.K., Galhotra, S., Chen, G.T.Y., Pelizzari, C.A., Beck, R.N., Chen, C.-T., Cooper, M.D., Mullan, J.F., Hekmatpanah, J. and Spire, J.-P.: The brain: Integrated three-dimensional display of MR and PET images. *Radiology* **172**:783-789, 1989.

J7. Lin, W.-C., Chen, S.-Y. and Chen, C.-T.: A new surface interpolation technique for reconstructing 3-D objects from serial cross-section. *Computer Vision, Graphics, and Image Processing* **48**:124-143, 1989.

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J11. Chen, C.-T., Johnson, V.E., Wong, W.H., Hu, X., Metz, C.E.: Bayesian image reconstruction in positron emission tomography. *IEEE Trans Nucl Sci* **NS-37**:636-641, 1990.

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J14. Chen, S.-Y., Lin, W.-C., and Chen, C.-T.: Split-and-merge image segmentation based on localized feature analysis and statistical test. *Graphical Models and Image Processing* **53**:457-475, 1991

J15. Lin, W.-C., Chen, S.-Y., and Chen, C.-T.: Automated surface interpolation techniques for 3-D object reconstruction from serial cross sections. *Computerized Medical Imaging and Graphics* **15**:265-276, 1991.

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J18. Hoffmann, K.R., Chen, C.-T., and Doi, K: Automated region identification and its application to measuring cardiac function. *Am, J. Cadiac Imag.* **15**:272-280, 1991.

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J24. Liang, C.-C., Lin, W.-C. and Chen, C.-T.: Intensity interpolation for reconstructing 3-D medical images from serial cross-section. (Submitted to *Computerized Medical Imaging and Graphics*)

J25. Chen, T., Lin, W.-C., and Chen, C.-T.: Artificial neural networks for 3-D motion analysis, Part I: Rigid motion. (Submitted to *IEEE Trans. Neural Network*).

J26. Chen, T., Lin, W.-C., and Chen, C.-T.: Artificial neural networks for 3-D motion analysis, Part II: Nonrigid motion. (Submitted to *IEEE Trans. Neural Network*).

J27. Liang, C.-C., Lin, W.-C., and Chen, C.-T.: Computational models for three-dimensional deformation processes. (Submitted to *CVGIP: Grphical Models and Image Processing*).

J28. Chen, S.-Y., Lin, W.-C., and Chen, C.-T.: An expert image analysis system for recognition of major brain structures. (Submitted to *IEEE Trans Med Imaging*).

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P25. Chen, C.-T., Pelizzari, C.A., Wong, W.H., Levin, D., and Cooper, M.: Sensor fusion in brain imaging. Presented at the XV International Symposium on Cerebral Blood Flow and Metabolism (Brain '91), June 1 - 6, 1991, Miami, Florida, USA, *J Cereb Blood Flow Metab* **11**(Suppl.2):S385, 1991.

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P33. Cooper, M., Metz, J.T., and Chen, C.-T.: Neurophysiological and cognitive studies by brain activation: methodological considerations and applications using PET. Presented at the 6th Symposium on the Medical Application of Cyclotrons, June 1 - 4, 1992, Turku, Finland. In: *Medical Application of Cyclotrons VI*, (L-M Voipio-Pulkki and U. Wegelius, eds.), Medica-Odontologica, Sarja-Ser.D, No. 88, Turun Yliopisto, Turku, Finland, pp. I37-I38, 1992.

P34. Chen, C.-T., Cooper, M., Metz, J.T., Chou, J.-S., Ordonez, C.E., Yu, X., Ouyang, X., and Yap, J.T.: Improvement of quantitative analysis of PET data by incorporation of spatially-correlated CT and MR images. Presented at the 6th Symposium on the Medical Application of Cyclotrons, June 1 - 4, 1992, Turku, Finland. In: *Medical Application of Cyclotrons VI*, (L-M Voipio-Pulkki and U. Wegelius, eds.), Medica-Odontologica, Sarja-Ser.D, No. 88, Turun Yliopisto, Turku, Finland, pp. A27-A28, 1992.

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Abstracts:

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A1. Pelizzari, C.A., Chen, G.T.Y., Halpern, H., Chen, C.-T. and Cooper, M.D.: Three-dimensional correlation of PET, CT and MR images. Presented at the 34th SNM Annual Meeting, June 1987. *J Nucl Med* **28**(4):682, 1987.

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