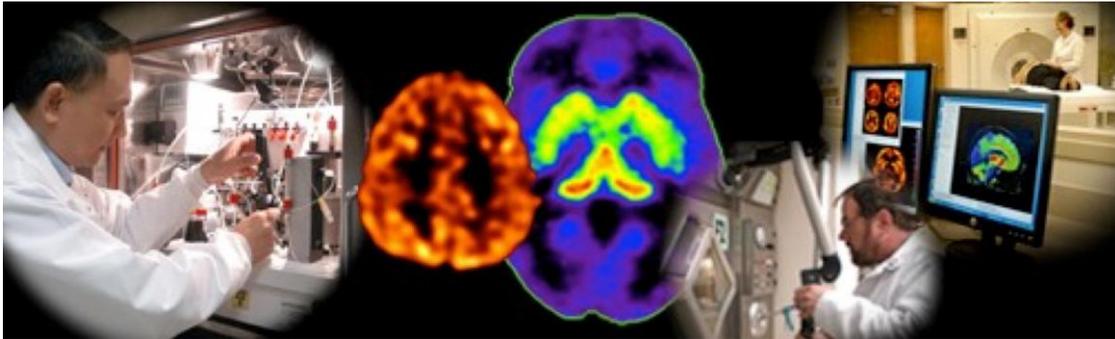


Yale University Positron Emission Tomography (PET) Center

<http://petcenter.yale.edu>

pet.center@yale.edu



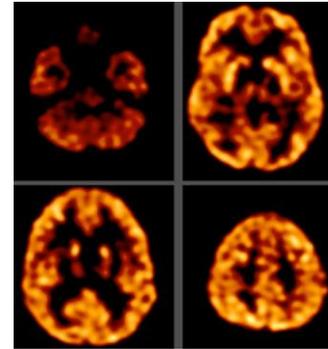
Overview: Yale PET Center Resources and Capabilities

- State-of-the-art facility operational since Spring 2006
- Expert faculty; experienced technologists/staff
- Research nurses on-site; physiological monitoring
- GE PETtrace cyclotron, targetry for producing C-11, F-18, N-13, O-15
- 3 clinical PET scanners including mCT PET/CT, HRRT- high resolution brain scanner, and HR+
- 3 scanners for small animal imaging: 2 Focus-220, Inveon PET/CT
- State-of-the-art motion correction
- Radiochemistry laboratory with modules to produce a wide variety of radiotracers
- Chemistry SOPs – high quality standards for safety, production, use
- cGMP (Good Manufacturing Practices compliant)
- Fully equipped laboratory for blood and metabolite analyses
- Image analysis laboratory and image analysis software applications
- Rapid turnaround of data (automatic)
- Collaborative opportunities (close proximity to Yale School of Medicine Departments, Research Centers, Yale-New Haven Hospital)

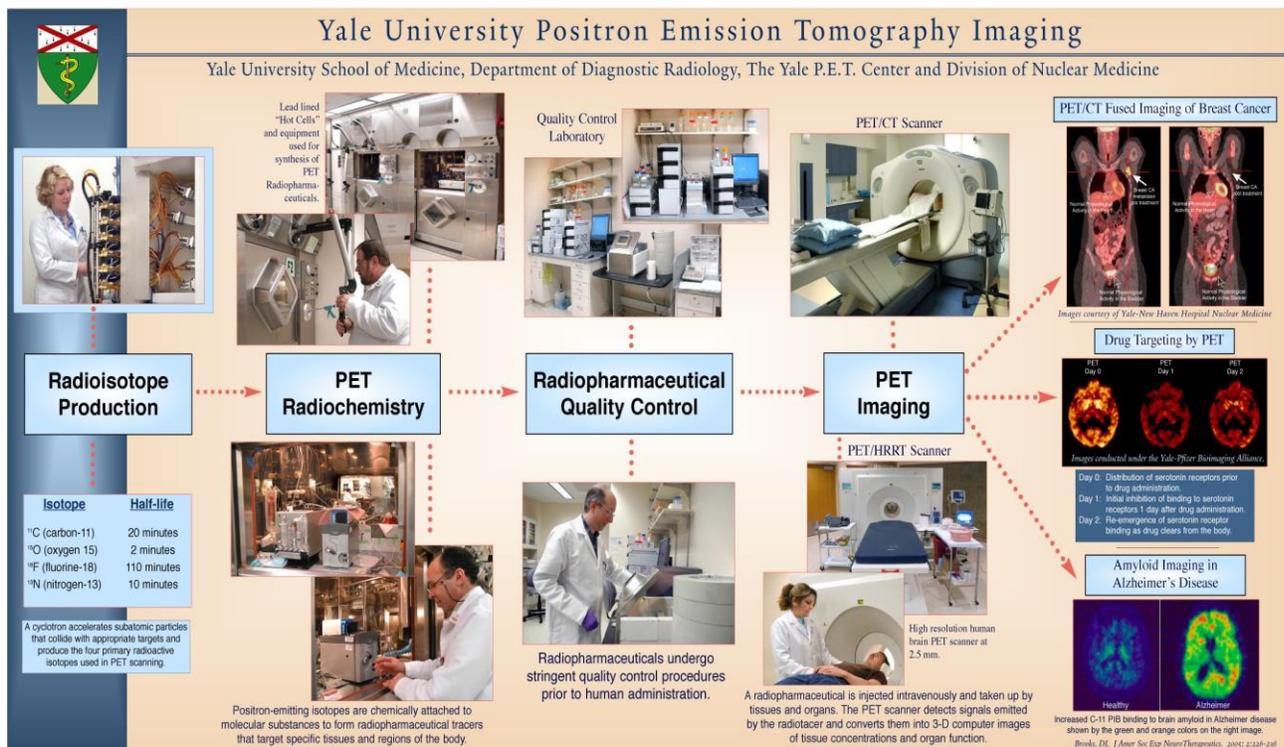
Background

What is PET?

Positron Emission Tomography (PET) is a non-invasive diagnostic imaging technique that provides researchers and clinicians with images of organ function (including blood flow, glucose metabolism, and concentrations of receptors, transporters, enzymes and other proteins in the brain and body tissues). During the PET scanning process, radioactive compounds called tracers are injected into the body where they are taken up by organs and tissues. The PET scanner picks up signals from the radioactive tracers and can detect biochemical changes in body tissues before structural damage occurs from disease. This information allows clinicians to be proactive in their treatments and assists researchers in detecting early biomarkers of disease that can aid diagnosis and advance drug development.



The PET Imaging Process



Overview of the Yale PET Center

In 2004, Yale University broke ground for a new, state-of-the-art Positron Emission Tomography (PET) Research Center dedicated to providing the highest quality of nuclear imaging research. Since officially opening in 2006, this 16,000 sq. ft. PET Center core facility has grown to include 55 scientists, technicians, and students who collaborate with Yale investigators from the fields of chemistry, physics, computer science, biomedical engineering, radiology, psychiatry, neurology, cardiology, internal medicine, and oncology. Collaborations with industry partners serve to advance the use of molecular imaging in new medication discovery and the development of new diagnostic PET radiopharmaceuticals.

The Yale University PET Center is comprised of a technologically advanced Radiochemistry Laboratory engaged in the development and use of a complete line of PET radiopharmaceuticals, and an Imaging and Data Analysis section that oversees scanning procedures and optimizes data acquisition and analysis.

PET Center Resources

- GE PETtrace cyclotron, with targetry for producing positron-emitting isotopes (^{11}C , ^{15}O , ^{13}N , and ^{18}F); 12 hot cells (6 full-sized hot cells and 6 mini-cells) containing dedicated radiochemistry modules for the production of a wide variety of radiotracers



- 6 Siemens PET scanners: mCT whole body PET/CT scanner, HR+ whole body scanner, high resolution HRRT scanner for brain imaging; 2 Focus 220 small animal scanners, and an Inveon microPET/CT



- Fully equipped laboratory for blood and metabolite analyses and an image analysis lab

Through the use of specific radiolabeled molecules and state-of-the-art scanning equipment, quantitative measurements of a wide range of physiological functions can be assessed in clinical and pre-clinical populations.

The work is intrinsically translational, as new radiopharmaceuticals are first evaluated in animals in advance of studies in human controls and patient populations. Subsequently, human results are correlated with PET studies in animal models to evaluate mechanisms of disease progression and drug action.

The Yale University PET Center currently performs over 1000 PET clinical and pre-clinical scans per year under a wide range of research protocols. To date, over 10,000 administrations of PET radiopharmaceuticals have been performed as part of quantitative *in vivo* PET studies. Over 100 different radiopharmaceuticals have been administered to human subjects or preclinical species (mouse, rat, dog, pig, and non-human primate), and 48 radiopharmaceuticals have been administered specifically to humans.

What PET Research is Going on at Yale?

Yale scientists are utilizing PET in pre-clinical and human research studies to examine brain activity and chemical mechanisms involved in diseases such as schizophrenia, depression, PTSD, Alzheimer's disease, epilepsy, alcohol dependence, substance abuse, and diabetes. Outside the brain, PET studies at Yale focus on cancer, diabetes, and cardiac applications.

The PET Center partners with the Yale Alzheimer's Disease Research Unit (ADRU) and industry sponsors to utilize PET tracers (including [¹¹C]PIB, [¹⁸F]florbetapir, and [¹⁸F]AV-1451) to assess novel treatment mechanisms that have the potential to arrest and reverse the course of Alzheimer's Disease.

Collaborations with Pharma

The Yale PET Center collaborates with industry partners on a variety of research initiatives including methodology studies, new tracer development, pre-clinical research, and clinical trials in healthy control subjects and patients.

See descriptions of some of our recent studies on the following pages:

Recent Yale University PET Studies & Findings:

The first human studies of synaptic density via PET imaging of the SV2A vesicle protein allow visualization of synaptic density in healthy and epileptic human brains in living patients. PET imaging of SV2A with [^{11}C]UCB-J provides new opportunities for routine monitoring of the brain (versus traditional approaches requiring autopsy) in patients with various neurological diseases, where synaptic loss or dynamic changes in density could provide clues to prognosis (Fig.1.). This tracer has now been used in more than 10 different patient populations, including epilepsy, Alzheimer's disease, PTSD, Parkinson's disease, depression, substance abuse, alcohol dependence, and multiple sclerosis.

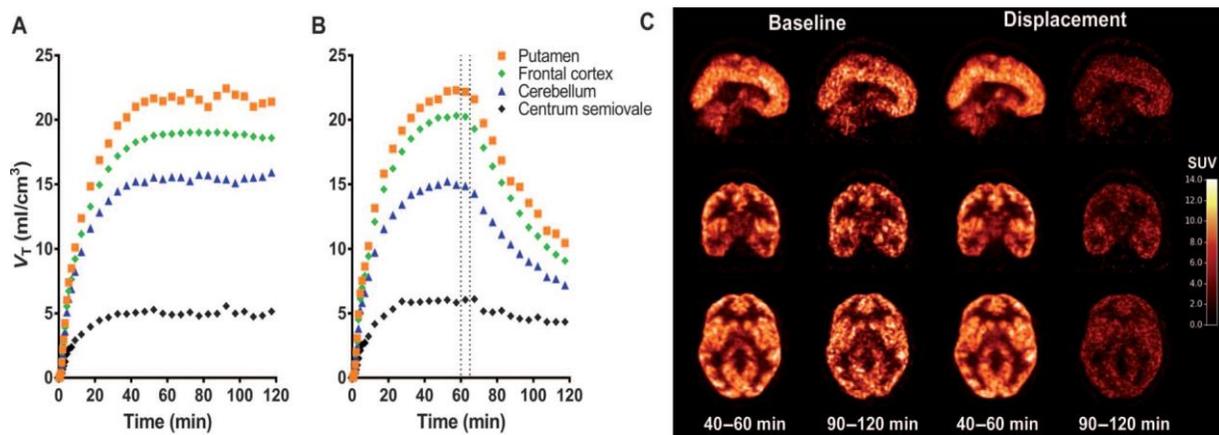


Fig.1. [^{11}C]UCB-J binds to SV2A in the healthy human brain.

(A and B) Regional time-activity curves in four brain regions after [^{11}C]UCB-J administration in 3 control subjects under baseline (A) or displacement conditions in which levetiracetam (1500mg) was intravenously infused 60 to 65min after the start of [^{11}C]UCB-J. *Finnema SJ, Nabulsi NB, Eid T, Detynecki K, Lin SF, Chen MK, Dhaher R, Matuskey D, Baum E, Holden D, Spencer DD, Mercier J, Hannestad J, Huang Y, Carson RE, Imaging synaptic density in the living human brain. Science Translational Medicine. 2016;8:348ra96.*

Loss of cannabinoid receptors observed in schizophrenia. Study utilizing [^{11}C]OMAR demonstrates that CB1R availability is lower in male SCZ subjects compared with HCs, and that antipsychotic and tobacco use may increase CB1R availability in this population. Thereby, supporting the hypothesis that alterations in the eCB system might contribute to the pathophysiology of SCZ. *Ranganathan M, Cortes-Briones J, Radhakrishnan R, Thurnauer H, Planeta B, Skosnik P, Gao H, Labaree D, Neumeister A, Pittman B, Surti T, Huang Y, Carson RE, D'Souza DC, Reduced Brain Cannabinoid Receptor Availability in Schizophrenia. Biol Psychiatry. 2016;79(12):997-1005.*

Decreased binding of [^{11}C]ABP688, a tracer for metabotropic glutamate receptor 5 (mGluR5), reflects downregulation/internalization. Ketamine-induced changes in mGluR5 availability in healthy and depressed subjects showed significant decreases in [^{11}C]ABP688 binding. These data support the development of mGluR5 therapies for depression. *Esterlis I, DellaGioia N, Pietrzak RH, Matuskey D, Nabulsi N, Abdallah CG, Yang J, Pittenger C, Sanacora G, Krystal JH, Parsey RV, Carson RE, DeLorenzo C, Ketamine-induced reduction in mGluR5 availability is associated with an antidepressant response: an [^{11}C]ABP688 and PET imaging study in depression, Mol Psychiatry, 2017 Apr 11.*

Novel network analysis of dopamine receptors in cocaine abuse. Study identified three distinct sources of receptors (binding potential, BP_{ND}), indicating lower intensity of a striatopallidal source and greater intensity of a pallidonigral source in cocaine use disorder. These patterns suggest cocaine-related alterations in dopamine receptors extend throughout the brain dopamine network (Fig.2.).

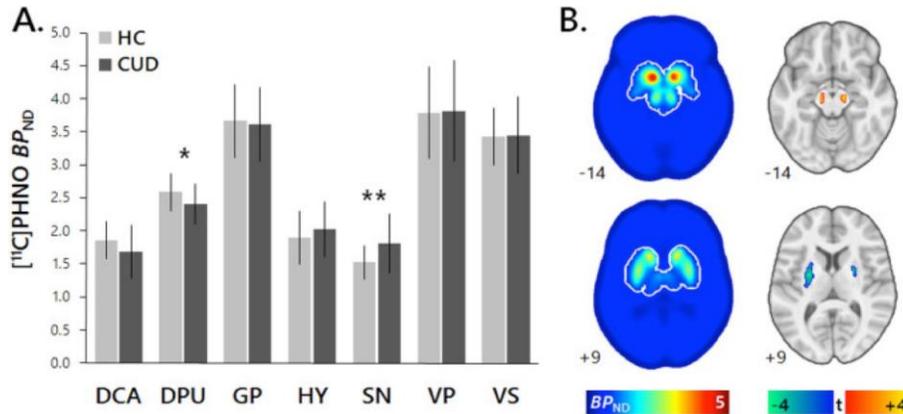


Fig.2. Regional analyses of [^{11}C]PHNO binding potential. (a) Region of interest analysis shows cocaine use (CUD) relative to healthy control (HC) participants had reduced BP_{ND} in the dorsal putamen (DPU) and greater BP_{ND} in the substantia nigra (SN). (b) Whole-brain analysis identified regions of where CUD relative to HC exhibited greater BP_{ND} in midbrain regions (red/yellow) and reduced BP_{ND} in the putamen (blue/green). *Worhunsky PD, Matuskey D, Gallezot JD, Gaiser EC, Nabulsi N, Angarita GA, Calhoun VD, Malison RT, Potenza MN, Carson RE, Regional and source-based patterns of [^{11}C]-(+)-PHNO binding potential reveal concurrent alterations in dopamine D2 and D3 receptor availability in cocaine-use disorder. Neuroimage. 2017;148:343-351.*

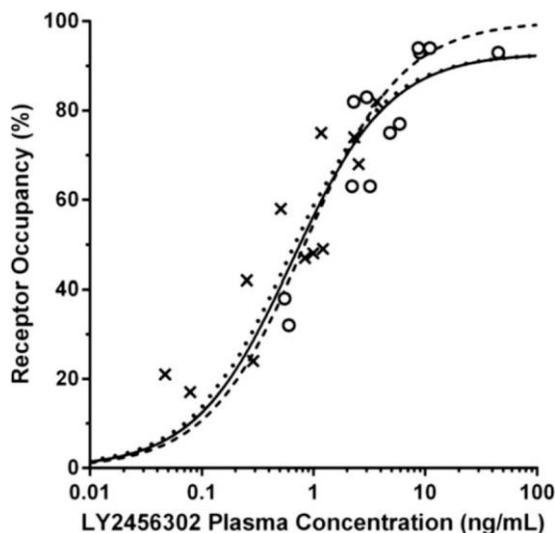


Fig.3. Relationship between drug concentration and kappa occupancy at 2.5 and 24 hours postdose are shown in circles and crosses, respectively. *Naganawa M, Dickinson GL, Zheng MQ, Henry S, Vandenhende F, Witcher J, Bell R, Nabulsi N, Lin SF, Ropchan J, Neumeister A, Ranganathan M, Tauscher J, Huang Y, Carson RE, Receptor Occupancy of the κ -Opioid Antagonist LY2456302 Measured with Positron Emission Tomography and the Novel Radiotracer ^{11}C -LY2795050, J Pharmacol Exp Ther, 356(2):260-266, 2016.*

Novel kappa opioid receptor (KOR) antagonist tracer found to be suitable for PET imaging and quantification of KOR in first in vivo evaluation of [^{11}C]-LY2795050 in humans. *Naganawa M, Zheng MQ, Nabulsi N, Tomasi G, Henry S, Lin SF, Ropchan J, Labaree D, Tauscher J, Neumeister A, Carson RE, Huang Y, Kinetic modeling of ^{11}C -LY2795050, a novel antagonist radiotracer for PET imaging of the kappa opioid receptor in humans, J Cereb Blood Flow Metab, 34:1818-1825, 2014.*

PET receptor occupancy study demonstrates that LY2456302, a kappa-opioid antagonist, penetrates the blood-brain barrier and blocks KOR in the brain in a dose-related manner. A dose of 10 mg of LY2456302 appears very well suited for further clinical testing (Fig.3.).

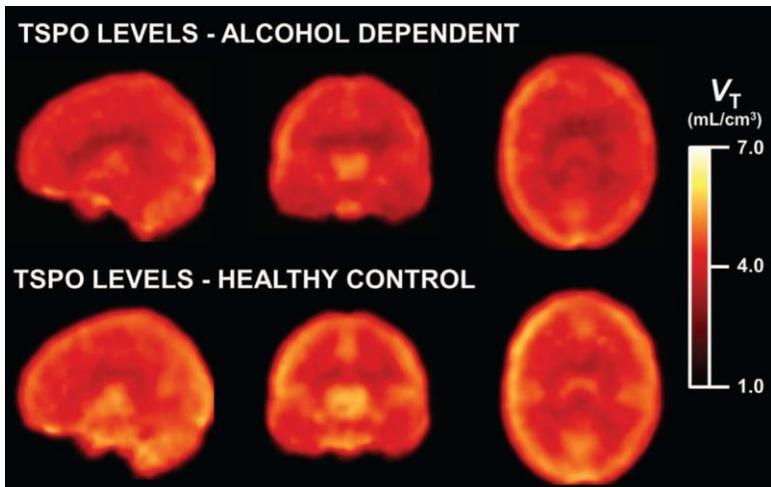


Fig.4. Average levels of activated microglia are lower in alcohol dependent subjects (top) compared with healthy controls (bottom). Hillmer AT, Sandiego CM, Hannestad J, Angarita GA, Kumar A, McGovern EM, Huang Y, O'Connor KC, Carson RE, O'Malley SS, Cosgrove KP, *In vivo* imaging of translocator protein, a marker of activated microglia, in alcohol dependence, *Mol Psychiatry*, 2017 Feb 28.

Changes in neuro-inflammation observed in alcohol dependence.

Study findings suggest alcohol dependence is associated with lower levels of activated microglia in the brain and a blunted immune response in the periphery (compared with healthy controls) as measured by [¹¹C]PBR28 PET (Fig.4.).

First demonstration in humans that a systemic LPS challenge induces robust increases in microglial activation in the brain.

Study measuring brain microglial activation with [¹¹C]PBR28 PET provides an approach to test new medications in humans for their putative anti-inflammatory effects (Fig.5.).

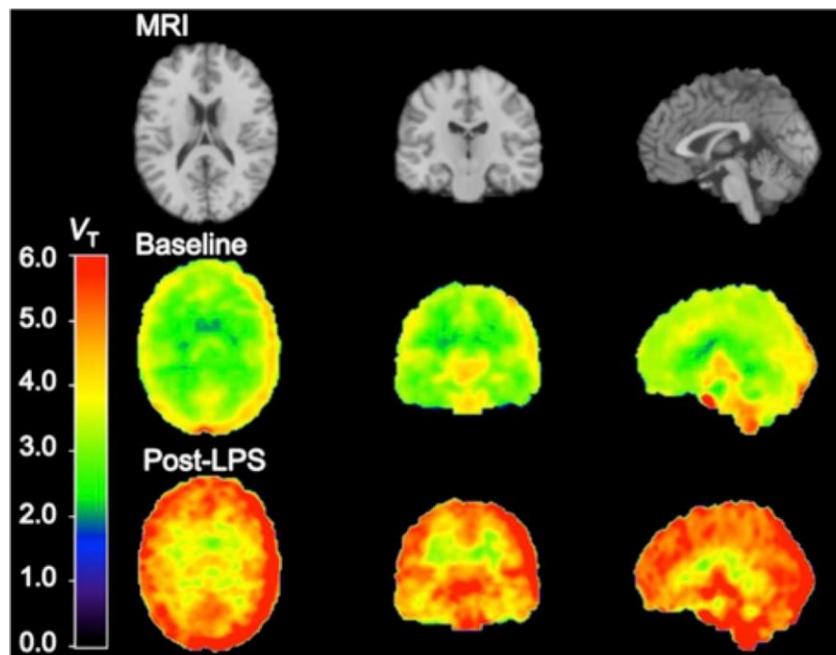


Fig.5. LPS administration significantly increases [¹¹C]PBR28 binding (V_T) from baseline in healthy control subjects. Average V_T images with the magnetic resonance image (MRI) shown for anatomical reference (Top row). Significance level was $*P < 0.01$ (linear mixed models) of the difference between baseline and post-LPS challenge scans. Sandiego CM, Gallezot JD, Pittman B, Nabulsi N, Lim K, Lin SF, Matuskey D, Lee JY, O'Connor KC, Huang Y, Carson RE, Hannestad J, Cosgrove KP, *Imaging robust microglial activation after lipopolysaccharide administration in humans with PET*, *Proc Natl Acad Sci USA*, 112:12468-12473, 2015.

PET imaging of ^{18}F -FP-DTBZ enables noninvasive and quantitative measurements of clinically relevant changes in pancreatic beta-cell mass (BCM), providing an opportunity to accelerate research on the pathophysiology of diabetes and revolutionize the preclinical development of new treatments, the clinical assessment of therapeutic efficacy, and the early diagnosis and subsequent monitoring of disease progression (Fig.6.).

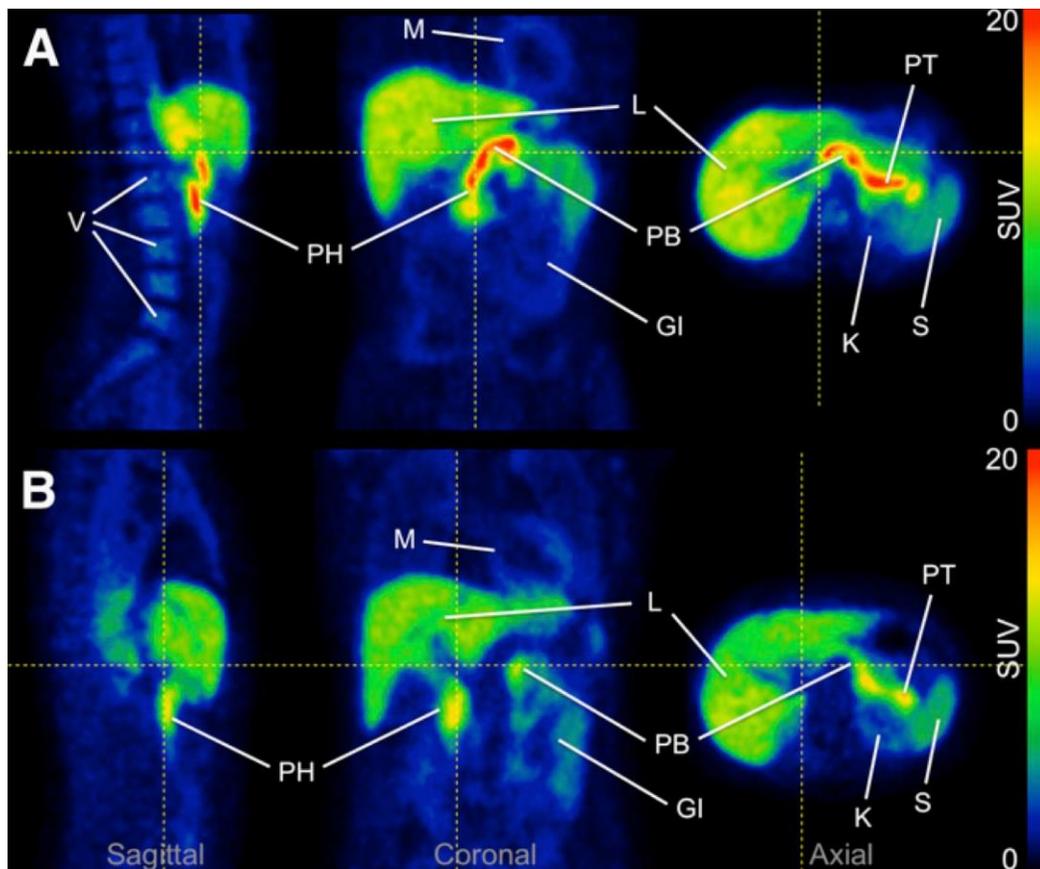


Fig.6. Representative ^{18}F -FP-DTBZ PET images. (A) Image acquired for healthy control subject showed high uptake of tracer in pancreas. (B) Pancreas uptake was reduced in type 1 diabetes patient. Both images represent PET data summed from 0 to 90 min after injection and are displayed on common scale (0–20 SUV—that is, radioactivity normalized by injected dose and body weight). GI gastrointestinal tract; K kidney; L liver; M myocardium; PB pancreas body; PH pancreas head; PT pancreas tail; S spleen; V vertebrae. Normandin MD, Petersen K, Ding YS, Lin SF, Naik S, Fowles K, Skovronsky DM, Herold KC, McCarthy TJ, Calle RA, Carson RE, Treadway JL, Cline GW, *In vivo* imaging of endogenous pancreatic Beta-cell mass in healthy and type 1 diabetic subjects using ^{18}F -fluoropropyl-dihydrotetrabenazine and PET, *J Nucl Med*, 53:908-916, 2012.

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Publications

Please see our web site:

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