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Prediction of arrhythmic events with positron emission tomography: PAREPET study design and methods.


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BACKGROUND: In medically-treated patients with ischemic cardiomyopathy, myocardial viability is associated with a worse prognosis than scar. The risk is especially great with hibernating myocardium (chronic regional dysfunction with reduced resting flow), and the excess mortality appears to be due to sudden cardiac death (SCD). Hibernating myocardium also results in sympathetic nerve dysfunction, which has been independently associated with risk of SCD. OBJECTIVES: PAREPET is a prospective, observational cohort study funded by NHLBI. It is designed to determine whether hibernating myocardium and/or inhomogeneity of sympathetic innervation by positron emission tomography imaging identifies patients with ischemic cardiomyopathy who are at high risk for SCD and cardiovascular mortality. METHODS: Patients with documented ischemic cardiomyopathy, an ejection fraction of <or=35%, and with no plans for coronary revascularization will be recruited. Major exclusion criteria include: history of resuscitated SCD, sustained VT, ICD discharge, or unexplained syncope; recent myocardial infarction (30 days), percutaneous coronary intervention (3 months), coronary bypass surgery (1 year); or comorbidities that would be expected to reduce life expectancy to <2 years. All patients will undergo transthoracic echocardiography, and dynamic cardiac positron emission tomography to quantify resting perfusion (13N-ammonia), norepinephrine uptake as an index of sympathetic innervation (11C-meta-hydroxyephedrine), and metabolic viability (18F-2-deoxyglucose during glucose-insulin clamp). The development of SCD or cardiovascular mortality will be determined by telephone follow-up every three months. In patients with an implantable cardiac defibrillator, appropriate device discharge will be considered a surrogate for SCD. CONCLUSION: The PAREPET study will prospectively determine whether the amount of viable dysfunction myocardium and/or cardiac sympathetic dysinnervation is associated with the risk of SCD. It is anticipated that the results of this trial will more specifically identify myocardial substrates of SCD. This will help target therapies intended to reduce arrhythmic death to those patients with the greatest likelihood of benefit.


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18F-Labeled p-fluorobenzyl triphenyl phosphonium cation (18F-FBnTP) is a member of a new class of positron-emitting lipophilic cations that may act as myocardial perfusion PET tracers. Here, we characterize the 18F-FBnTP uptake and retention kinetics, in vitro and in vivo, as well as the myocardial and whole-body biodistribution in healthy dogs, using PET. METHODS: Time-dependent accumulation and retention of 18F-FBnTP in myocytes in vitro was studied. Seven anesthetized, mongrel dogs underwent dynamic PET scans of the heart after intravenous administration of 126-240 MBq 18F-FBnTP. In 4 of the 7 dogs, at the completion of a 60-min dynamic scan, whole-body scans (4 bed positions, 5-min emission and 3-min transmission per bed) were acquired. Arterial blood samples were collected at 0, 5, 10, 20, 30, and 60 min after administration. Plasma activity was counted, and high-performance liquid chromatographic analyses for metabolites were performed. The extent of defluorination was assessed by measuring 18F-FBnTP bone uptake in mice, compared with 18F-fluoride. RESULTS: The metabolite fraction comprised <5% of total activity in blood at 5 min and gradually increased to 25% at 30 min after injection. In vivo, 18F-FBnTP myocardial concentration reached a plateau level within a few minutes, which was retained throughout the scanning time. In contrast, activity in the blood pool and lungs cleared rapidly (half-life = 19.5 +/- 4.4 and 30.7 +/- 11.6 s, respectively). Liver uptake did not exceed the activity measured in the myocardium. At 60 min, the uptake ratios of left ventricular wall to blood, lung, and liver (mean of 7 dogs) were 16.6, 12.2, and 1.2, respectively. Summation of activity from 5 to 15 min and from 30 to 60 min after injection produced high-quality cardiac images of similar contrast. Circumferential sampling and a polar plot revealed a uniform distribution, near unitary value, throughout the entire myocardium. The mean coefficient of variance, on 30- to 60-min images along the septum-to-anterior wall and the apex-to-base axes was 7.58% +/- 1.04% and 6.11% +/- 0.89% (mean +/- SD; n = 7), respectively, and on 5- to 15-min images was 7.25% +/- 1.43% and 6.12% +/- 1.88%, respectively. 18F-FBnTP whole-body distribution was highly organ specific with the kidney cortex being the major target organ, followed by the heart and the liver. CONCLUSION: 18F-FBnTP is a promising new radionuclide for cardiac imaging using PET with rapid kinetics, uniform myocardial distribution, and favorable organ biodistribution.


Weinmann P.
Reversible inverse mismatch in transient left ventricular apical ballooning: perfusion/metabolism positron emission tomography imaging.

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The central circulation in congestive heart failure non-invasively evaluated with dynamic positron emission tomography.


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BACKGROUND: Positron emission tomography (PET) with [15O]-H2O-PET (WAT-PET) or [11C]-acetate (AC-PET) quantifies myocardial perfusion and oxidative metabolism, but routine clinical use is hampered by the need for additional investigations to assess cardiac performance. OBJECTIVE: To apply classical tracer kinetics to dynamic PET could provide important haemodynamic parameters. METHODS: First-pass PET data were used with indicator dilution techniques to measure stroke volume index (SVI). Early pulmonary retention of [11C]-acetate was converted to standard uptake values (SUV) (Lung(AC-SUV)). Regional lung water (rLW) content was computed from the WAT-PET scan at equilibrium. PET was compared with radionuclide angiography and echocardiography in patients with ischaemic cardiomyopathy with New York Heart Association class II (n = 10) or III (n = 18) congestive heart failure. Elderly male volunteers without heart disease (n = 11) underwent AC-PET as controls. RESULTS: SVI with both tracers correlated in patients (r = 0.91, P<0.001, estimated standard error = 4 ml m(-2)) and with left ventricular ejection fraction (both tracers r>0.6, P<0.001). SVI was significantly different between all groups (ANOVA: P<0.001). Lung(AC-SUV) correlated with rLW (r = 0.78, P<0.001) and both were elevated in severe heart failure (P<0.05 for both). Elevated Lung(AC-SUV) was associated with a restrictive left ventricular (LV) filling pattern by Doppler echocardiography. CONCLUSION: Dynamic PET with first-pass analysis and tracers of myocardial perfusion enables quantification of the haemodynamic consequences of LV systolic and diastolic dysfunctions in ischaemic cardiomyopathy and could be useful in the evaluation of the central circulation in heart failure.

 Occupational radiation dose associated with Rb-82 myocardial perfusion positron emission tomography imaging.

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BACKGROUND: We determined staff radiation dose during rest and stress rubidium 82 myocardial perfusion positron emission tomography (PET) imaging. METHODS AND RESULTS: Patients received 1,587 +/- 163 MBq (42.9 +/- 4.4 mCi) Rb-82 during rest or pharmacologic stress. A pressurized ion chamber was used to monitor radiation exposure in 50 examinations. For comparison, staff exposure during pharmacologic stress in 20 other patients receiving 1,204 +/- 55.5 MBq (32.54 +/- 1.5 mCi) technetium 99m 2-methoxy isobutyl isonitrile (MIBI) was measured. For Rb-82 infusion and PET acquisition, the mean dose was 0.45 +/- 0.25 microSv (0.045 +/- 0.025 mrem). Exposure for routine stress testing at variable distances from the patient was equivalent to background. Similar exposure for pharmacologic stress testing through 7 minutes after injection of Tc-99m MIBI at variable distances was 1.075 +/- 0.32 microSv (0.108 +/- 0.03 mrem). However, exposure for stress tests starting 7 minutes after Rb-82 infusion at 0.5 m was estimated at 0.4 microSv (0.04 mrem). To determine the potential radiation dose for those responding to a medical emergency or otherwise in close proximity to a patient, we measured the mean cumulative dose at 0.5 m from 0 to 7 minutes of Rb-82 infusion, which resulted in 19.1 +/- 5.8 microSv (1.9 +/- 0.58 mrem). CONCLUSIONS: Radiation doses for all tasks during routine Rb-82 stress-rest PET are lower than measured Tc-99m MIBI values. However, the radiation dose in close proximity to the patient during or immediately after Rb-82 infusion can be considerably higher, underscoring the need for strict attention to source distance and contact times.
Self-Reported Fatigue Common among Optimally Treated HIV Patients: No Correlation with Cerebral FDG-PET Scanning Abnormalities.


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Objective: It was the aim of this study to determine the prevalence and severity of fatigue among optimally treated HIV patients and to investigate the potential association with systemic inflammation and abnormalities of the distribution of cerebral glucose metabolism. Methods: A cohort of HIV patients (n = 95), known to be HIV positive for 5 years, on antiretroviral therapy for a minimum of 3 years and with CD4 counts above 0.2 x 10(9) cells/l, completed a validated fatigue inventory, and plasma was analysed for pro-inflammatory markers including tumour necrosis factor-alpha, interleukin 6 and soluble urokinase receptor (suPAR) levels. The distribution of the regional cerebral metabolic rate of glucose was measured in a sub-group of patients suffering from severe fatigue (n = 9) and a group with no fatigue (n = 7) using fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) scanning. Results: Fifteen percent suffered from severe fatigue, but no association with pro-inflammatory markers was found. About 50% of the FDG-PET-scanned patients showed minor abnormalities in the relative cerebral metabolic rate of glucose. These abnormalities were not associated with fatigue but tended to correlate with a short HIV history (p = 0.058), a low CD4 nadir (p = 0.082) and elevated tumour necrosis factor-alpha levels (p = 0.074). Conclusion: Fatigue is common among optimally treated HIV patients. FDG-PET-described signs of imminent neurodegeneration among HIV patients who had a low CD4 nadir may illustrate an aspect of HIV neuropathogenicity. Copyright (c) 2006 S. Karger AG, Basel.

An extended simplified reference tissue model for the quantification of dynamic PET with amphetamine challenge.


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BACKGROUND:: Equilibrium analysis to quantify dynamic positron emission tomography (PET) with bolus followed by continuous tracer infusion and acute amphetamine challenge assumes that all tissue kinetics attain steady states during pre- and post-challenge phases. Violations of this assumption may result in unreliable estimation of the amphetamine-induced percent change in the binding potential (DeltaBP%). METHOD:: We derived an extended simplified reference tissue model (ESRTM) for modeling tracer kinetics in the pre- and post-challenge phases. Ninety-minute [(11)C]raclopride PET studies with bolus injection followed by continuous tracer infusion were performed on 18 monkeys and 2 baboons. Forty minutes after the bolus injection, a single acute intravenous amphetamine administration was given of 2.0 mg/kg to monkeys and of 0.05, 0.1, 0.5, and 1.5 mg/kg to baboons. Computer simulations further evaluated and characterized the ESRTM.

RESULTS:: In monkey studies, the DeltaBP% estimated by the ESRTM was 32±/-11, whereas, the DeltaBP% obtained using the equilibrium methods was 32% to 81% lower. In baboon studies, the DeltaBP% values estimated with the ESRTM showed a linear relationship between the DeltaBP% and the natural logarithm of amphetamine dose (R(2)=0.96), where the DeltaBP%=10.67Ln(dose)+33.79 (0.05<==dose in mg/kg<==1.5). At 1.5 mg/kg amphetamine, the DeltaBP% estimates from equilibrium methods were 18% to 40% lower than those estimated by the ESRTM. Results showed that the nonsteady state of tracer kinetics produced an underestimation of the DeltaBP% from the equilibrium analysis. The accuracy of the DeltaBP% estimates from the equilibrium analysis was significantly improved by the ESRTM. The DeltaBP% estimated by the ESRTM in the study was consistent with that from previous [(11)C]raclopride PET with amphetamine challenge.

CONCLUSION:: In conclusion, the ESRTM is a robust kinetic modeling approach and is proposed for the quantification of dynamic PET with acute amphetamine stimulation.

Predicting brain concentrations of drug using positron emission tomography and venous input: modeling of arterial-venous concentration differences.

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OBJECTIVE: In a positron emission tomography (PET) study, the concentrations of the labeled drug (radiotracer) are often different in arterial and venous plasma, especially immediately following administration. In a PET study, the transfer of the drug from plasma to brain is usually described using arterial plasma concentrations, whereas venous sampling is standard in clinical pharmacokinetic studies of new drug candidates. The purpose of the study was to demonstrate the modeling of brain drug kinetics based on PET data in combination with venous blood sampling and an arterio-venous transport (T(ave)).

METHODS: Brain kinetics (C(br)) was described as the convolution of arterial plasma kinetics (C(ave)) with an arterial-to-brain impulse response function (T(br)). The arterial plasma kinetics was obtained as venous plasma kinetics (C(ave)) convolved with the inverse of the arterio-venous transform (T(ave) (-1)). The brain kinetics was then given by C(br)=C(ave)*T(ave) (-1)*T(br). This concept was applied on data from a clinical PET study in which both arterial and venous plasma sampling was done in parallel to PET measurement of brain drug kinetics. The predictions of the brain kinetics based on an arterial input were compared with predictions using a venous input with and without an arterio-venous transform. RESULTS: The venous
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Based models for brain distribution, including a biexponential arterio-venous transform, performed comparably to models based on arterial data and better than venous based models without the transform. It was also shown that three different brain regions with different shaped concentration curves could be modeled with a common arterio-venous transform together with an individual brain distribution model. **CONCLUSION:** We demonstrated the feasibility of modeling brain drug kinetics based on PET data in combination with venous blood sampling and an arterio-venous transform. Such a model can in turn be used for the calculation of brain kinetics resulting from an arbitrary administration mode by applying this model on venous plasma pharmacokinetics. This would be an important advantage in the development of drugs acting in the brain, and in other circumstances when the effect is likely to be closer related to the brain than the plasma concentration.

**Stereotactic Imaging for Radiosurgery: Localization Accuracy of Magnetic Resonance Imaging and Positron Emission Tomography Compared with Computed Tomography.**


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Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) provide complementary information for treatment planning in stereotactic radiosurgery. We evaluated the localization accuracy of MRI and PET compared with CT. Two kinds of planning frame (Elekta, Tokyo) were developed. Deviations of measured coordinates at target points (x = 50, 100, 150; y = 50, 100, 150) were determined on different axial planes (z = 30-140 for MRI and CT study and Z = 50-120 for PET and CT study). For MRI, the deviations were no more than 0.8 mm in each direction. For PET, the deviations were no more than 2.7 mm. For both imaging modalities studied, accuracy was at or below the imaging resolution (pixel size) and should be considered useful for clinical stereotactic planning purposes. Copyright (c) 2006 S. Karger AG, Basel.

**The physiological and pathophysiological roles of neuronal histamine: An insight from human positron emission tomography studies.**

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Histamine neurons are exclusively located in the posterior hypothalamus, and project their fibers to almost all regions of the human brain. Although a significant amount of research has been done to clarify the functions of the histaminergic neuron system in animals, a few studies have been reported on the roles of this system in the human brain. In past studies, we have been able to clarify some of the functions of histamine neurons using different methods, such as histamine-related gene knockout mice or human positron emission tomography (PET). The histaminergic neuron system is known to modulate wakefulness, the sleep-wake cycle, appetite control, learning, memory and emotion. Accordingly we have proposed that histamine neurons have a dual effect on the CNS, with both stimulatory and suppressive actions. As a stimulator, neuronal histamine is one of the most important systems that stimulate and maintain wakefulness. Brain histamine also functions as a suppressor in bioprotection against various noxious and unfavorable stimuli of convulsion, drug sensitization, denervation supersensitivity, ischemic lesions and stress susceptibility. This review summarizes our works on the functions of histamine neurons using human PET studies, including the development of radiolabeled tracers for histamine H1 receptors (H1R: (11)C-doxepin and (11)C-pyrilamine), PET measurements of H1R in depression, schizophrenia, and Alzheimer's disease (AD), and studies on the sedative effects of antihistamines using H2(15)O and H1R occupancy in the human brain. These molecular and functional PET studies in humans are useful for drug development in this millennium.

**Functional neuroimaging in the preoperative evaluation of children with drug-resistant epilepsy.**

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**FUNCTIONAL NEUROIMAGING:** Although the primary imaging modality in the management of epilepsy is magnetic resonance imaging MRI, functional neuroimaging with positron-emission tomography (PET) and single photon emission computed tomography (SPECT) often provides complementary information and, in a number of situations, provides unique information that cannot be obtained with MRI. The most commonly used PET tracers used for epilepsy evaluation are 2-deoxy-2-[(18)F]fluoro-D-glucose (FDG) and [(11)C]flumazenil (FMZ). Recently, interictal PET with alpha-[((11)C]methyl-L-tryptophan was found to be highly specific for the epileptic focus and can differentiate between epileptogenic and nonepileptogenic lesions in the same patient (e.g., in patients with tuberous sclerosis). **DISCUSSION:** In this review, we discuss clinical applications of these three PET tracers in drug-resistant temporal and extratemporal lobe epilepsy, selected epilepsy syndromes of childhood, lesional and nonlesional epilepsy, and the challenges of imaging secondary epileptic foci. A brief discussion of SPECT applications in epilepsy is also included. With further development of new tracers highly sensitive and specific for epileptogenic brain regions, the presurgical evaluation of refractory epilepsy will be greatly facilitated. Approximately 0.5 to 1.0% of the population suffer from epilepsy, of which 15-20% are intractable. Infants and children, whose seizures have a focal onset are refractory to anticonvulsants and are prolonged, tend to have the worst cognitive outcome [Meador KJ, Neurology 58 (Suppl 5):S21-S26, 2002]. Seizures themselves affect the developing brain and contribute to an adverse neurologic outcome (Holmes, Pediatric Neurology 33:1-110, 2005). **CONCLUSION:** Therefore,
C-nicotine binding. OBJECTIVES: To investigate the relationship between measures of cognitive function and in vivo using neuropsychological tests of global cognition, episodic memory, attention, and visuospatial ability. RESULTS: Mean (S)(-)(11)C-nicotine was used to assess nicotine binding sites in the brain by PET. Cognitive function was assessed in mild AD patients. A dual tracer model with administration of (15)O-water for regional cerebral blood flow (11)C-nicotine binding in mild AD brain as assessed by PET. MATERIALS AND METHODS: Twenty-seven patients with cognitive function. Positron emission tomography (PET) has so far been used to visualize neuronal nAChRs in vivo by postmortem AD brain tissue. The alpha(4) and alpha(7) nAChR subunits were suggested to play an important role in cognitive development.

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Functional imaging studies with positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown alterations in glucose metabolism, perfusion, dopaminergic systems, cholinergic systems and activation of microglia in the brains of patients with Parkinson's disease (PD), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and multiple system atrophy (MSA). [(18)F]fluorodeoxyglucose-PET and perfusion SPECT show characteristic changes in brain glucose metabolism and perfusion, which are useful for differential diagnosis of these disorders. [(18)F]dopa-PET and SPECT studies of dopamine transporters show marked impairment of nigrostriatal neuronal terminals in PD, PSP, CBD and MSA. PET studies with carbon-11-labeled acetylcholine analogs have shown mild to moderate reduction of acetylcholinesterase (AChE) activity in the cerebral cortex in PD, severe reduction of AChE activity in the thalamus in PSP, and marked reduction of AChE activity in the cerebellum. [(11)C][R]-PK11195-PET studies have shown an increase in activated microglia in brain regions that mirror the known distribution of neuropathologic changes in PD, CBD and MSA, which provides insight into the pathophysiology of these disorders.


Age-related decline of dopamine synthesis in the living human brain measured by positron emission tomography with L-[beta-11C]DOPA.

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Loss of dopamine synthesis in the striatum with normal human aging has been observed in the postmortem brain. To investigate whether there is age-associated change in dopamine synthesis in the extrastriatal brain regions similar to that in the striatum, positron emission tomography studies with (11)C-labelled l-DOPA were performed on 21 normal healthy male subjects (age range 20-67 years). Decline in the tissue fraction of gray matter per region of interest was also investigated. The overall uptake rate constant for each region of interest was quantified by the Patlak plot method using the occipital cortex as reference region. Regions of interest were set on the dorsolateral prefrontal cortex, lateral temporal cortex, medial temporal cortex, occipital cortex, parietal cortex, anterior cingulate, thalamus, midbrain, caudate nucleus, and putamen. Test-retest analysis indicated good reproducibility of the overall uptake rate constant. Significant age-related declines of dopamine synthesis were observed in the striatum and extrastriatal regions except midbrain. The decline in the overall uptake rate constant was more prominent than in the tissue fraction of gray matter. These results indicate that the previously demonstrated age-related decline in striatal dopamine synthesis extends to several extrastriatal regions in normal human brain.

Psychopharmacology (Berl). 2006 Jul 11

PET imaging of cortical (11)C-nicotine binding correlates with the cognitive function of attention in Alzheimer's disease.


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RATIONALE: Patients suffering from Alzheimer's disease (AD) experience a marked reduction in cortical nicotinic acetylcholine receptors (nAChRs). In particular, selective loss of the alpha(4)beta(2) nAChR subtype was observed in postmortem AD brain tissue. The alpha(4) and alpha(7) nAChR subunits were suggested to play an important role in cognitive function. Positron emission tomography (PET) has so far been used to visualize neuronal nAChRs in vivo by (11)C-nicotine binding. OBJECTIVES: To investigate the relationship between measures of cognitive function and in vivo (11)C-nicotine binding in mild AD brain as assessed by PET. MATERIALS AND METHODS: Twenty-seven patients with mild AD were recruited in this study. A dual tracer model with administration of (15)O-water for regional cerebral blood flow and [(S)-]-(11)C-nicotine was used to assess nicotine binding sites in the brain by PET. Cognitive function was assessed using neuropsychological tests of global cognition, episodic memory, attention, and visuospatial ability. RESULTS: Mean cortical (11)C-nicotine binding significantly correlated with the results of attention tests [Digit Symbol test (r=-0.44 and p=0.02) and Trail Making Test A (TMT-A) (r=0.42 and p=0.03)]. No significant correlation was observed between (11)C-nicotine binding and the results of tests of episodic memory or visuospatial ability. Regional analysis showed that (11)C-nicotine binding in the frontal and parietal cortex, which are the main areas for attention, correlated significantly with the Digit Symbol test and TMT-A results. CONCLUSION: Cortical nicotinic receptors in vivo in mild AD patients are robustly associated with the cognitive function of attention.
Comparative assessment of statistical brain MR image segmentation algorithms and their impact on partial volume correction in PET.

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Magnetic resonance imaging (MRI)-guided partial volume effect correction (PVC) in brain positron emission tomography (PET) is now a well-established approach to compensate the large bias in the estimate of regional radioactivity concentration, especially for small structures. The accuracy of the algorithms developed so far is, however, largely dependent on the performance of segmentation methods partitioning MRI brain data into its main classes, namely gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). A comparative evaluation of three brain MRI segmentation algorithms using simulated and clinical brain MR data was performed, and subsequently their impact on PVC in (18)F-FDG and (18)F-DOPA brain PET imaging was assessed. Two algorithms, the first is bundled in the Statistical Parametric Mapping (SPM2) package while the other is the Expectation Maximization Segmentation (EMS) algorithm, incorporate a priori probability images derived from MR images of a large number of subjects. The third, here referred to as the HBSA algorithm, is a histogram-based segmentation algorithm incorporating an Expectation Maximization approach to model a four-Gaussian mixture for both global and local histograms. Simulated under different combinations of noise and intensity non-uniformity, MR brain phantoms with known true volumes for the different brain classes were generated. The algorithms' performance was checked by calculating the kappa index assessing similarities with the "ground truth" as well as multiclass type I and type II errors including misclassification rates. The impact of image segmentation algorithms on PVC was then quantified using clinical data. The segmented tissues of patients' brain MRI were given as input to the region of interest (ROI)-based geometric transfer matrix (GTM) PVC algorithm, and quantitative comparisons were made. The results of digital MRI phantom studies suggest that the use of HBSA produces the best performance for WM classification. For GM classification, it is suggested to use the EMS. Segmentation performed on clinical MRI data show quite substantial differences, especially when lesions are present. For the particular case of PVC, SPM2 and EMS algorithms show very similar results and may be used interchangeably. The use of HBSA is not recommended for PVC. The partial volume corrected activities in some regions of the brain show quite large relative differences when performing paired analysis on 2 algorithms, implying a careful choice of the segmentation algorithm for GTM-based PVC.


Net influx of plasma 6-[18F]fluoro-L-DOPA (FDOPA) to the ventral striatum correlates with prefrontal processing of affective stimuli.


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Dopaminergic neurotransmission in the ventral and dorsal striatum interact with central processing of rewarding and reward-indicating stimuli, and may affect frontocortical-striatal-thalamic circuits regulating goal-directed behaviour. Thirteen healthy male volunteers were investigated with multimodal imaging, using the radioligand 6-[18F]fluoro-L-DOPA (FDOPA) for positron emission tomography (PET) measurements of dopamine synthesis capacity, and also functional magnetic resonance imaging (fMRI) in a cognitive activation paradigm. We calculated the correlation between FDOPA net blood-brain influx (ml/g/min) in the ventral and associative dorsal striatum and BOLD signal changes elicited by standardized affectively positive, negative and neutral visual stimuli. The magnitude of the ventral striatum was positively correlated with BOLD signal increases in the left anterior cingulate cortex and right insular operculum elicited by positive vs. neutral stimuli, but not negative vs. neutral stimuli. In the dorsal striatum, the magnitude of was positively correlated with processing of positive and negative stimuli in the left dorsolateral prefrontal cortex. These findings suggest that dopamine synthesis capacity in the ventral striatum correlates with the attentional processing of rewarding positive stimuli in the anterior cingulate cortex of healthy subjects. Dopaminergic neurotransmission in the associative dorsal striatum has been associated previously with habit learning. The observed correlation between dopamine synthesis capacity in the dorsal striatum and BOLD signal changes in the dorsolateral prefrontal cortex suggests dopaminergic modulation of processing of emotional stimuli in brain areas associated with motor planning and executive behaviour control.


Comparison of the diagnostic performance of FDG-PET and VBM-MRI in very mild Alzheimer's disease.


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PURPOSE: The aim of this study was to compare the diagnostic performance of (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and voxel-based morphometry (VBM) on magnetic resonance imaging (MRI) in the same group of patients with very mild Alzheimer's disease (AD). METHODS: Thirty patients with very mild AD (age 67.0 +/- 5.8 years; MMSE score 25.5 +/- 1.2, range 24-28); 32 patients with mild AD (age 67.0 +/- 4.5 years, MMSE score 22.1 +/- 0.8, range 21-23) and 60 age- and sex-matched normal volunteers underwent both FDG-PET and three-dimensional spoiled gradient echo MRI. Statistical parametric mapping was used to conduct voxel by voxel analysis and Z score mapping. First, the region of interest (ROI) maps of significant reductions in glucose metabolism and grey matter density in the mild AD patients were
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defined. Secondly, analysis of receiver operating characteristic (ROC) curves for Z scores in the ROI maps discriminating very mild AD patients and normal controls was performed. RESULTS: In mild AD patients, FDG-PET indicated significant reductions in glucose metabolism in the bilateral posterior cingulate gyri and the right parietotemporal area, while VBM analysis showed a significant decrease in grey matter volume density in the bilateral amygdala/hippocampus complex, compared with the normal control group. ROC analysis showed that in very mild AD patients the accuracy of FDG-PET diagnosis was 89% and that of VBM-MRI diagnosis was 83%. The accuracy of the combination of FDG-PET and VBM-MRI diagnosis was 94%. CONCLUSION: In very mild AD, both FDG-PET and VBM-MRI had high accuracy for diagnosis, but FDG-PET showed slightly higher accuracy than VBM-MRI. Combination of the two techniques will yield a higher diagnostic accuracy in very mild AD by making full use of functional and morphological images.


Mapping the relative contribution of gray matter activity vs. volume in brain PET: a new approach.

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Interpretation of brain positron emission tomography (PET) in terms of function vs. structure is ambiguous owing to the partial volume effect (PVE). Therefore, observed differences in tracer distribution could reflect differences in either activity or volume, a problem that applies principally to gray matter (GM) since white matter (WM) virtually always has uniform activity. To assess the contribution of GM volume vs. activity, we implemented a method to directly compare PET images with underlying structure, and applied it to resting-state (18)Fluoro-deoxy-glucose-PET (FDG) of healthy subjects. Methods. Average GM and WM PVE-corrected mean FDG uptake values were applied onto co-registered segmented magnetic resonance imaging data sets to generate a "virtual PET" in which activity is proportional to GM volume and resolution set to that of PET. The raw PET and virtual PET values were then compared across the sample of subjects, first voxel-wise to detect clusters with significant activity-volume mismatch, and second within regions-of-interest (ROI) to quantify mismatches between unsmoothed voxel values. Results. Relative to volume, there was significant hyperactivity of most GM structures of the dorsal brain—except the thalamus—and significant hypovascularity of the temporal lobe, hippocampal region, and cerebellum, consistent across the voxel- and ROI-based analyses. Conclusion. As applied to normals, our method documented the expected contribution of functional activity independently of local differences in GM volume in the normal pattern of FDG uptake, and disclosed marked heterogeneities in functional activity per unit GM volume among structures. This generic method should find applications in pathological states as well as for other PET and SPECT radiotracers.


Congenital perisylvian syndrome: MRI and glucose PET correlations.

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Congenital perisylvian syndromes are late migration/cortical organization disorders associated with distinctive clinical and imaging features. The clinical, magnetic resonance imaging, and 2-deoxy-2-[18F] fluoro-D-glucose (FDG) positron emission tomography scan findings of six children (age range: 3.2-16.7 years; 5 males) with congenital perisylvian syndrome were evaluated. The patients presented with heterogenous neurologic impairments, depending upon the involved hemisphere and the extension of perisylvian malformation. Two manifested bilateral malformation and four manifested unilateral. The characteristic MRI finding consisting of a vertically oriented sylvian fissure continuous with the central and postcentral sulcus was associated with variable extension of bordering polymicrogyric cortex. The positron emission tomography scans of all patients revealed perisylvian metabolic abnormalities corresponding to the magnetic resonance imaging-defined abnormality. Variable extent of abnormal glucose metabolism was also observed in areas with normal magnetic resonance imaging features. All patients with unilateral magnetic resonance imaging abnormality exhibited abnormal glucose metabolism also in the contralateral side. The two patients with bilateral malformation had more extensive positron emission tomography abnormalities than the morphologic anomalies on MRI. Although MRI remains the diagnostic gold standard to detect the lesion, positron emission tomography scan is helpful to evaluate the full functional extension of the cortical anomaly, thereby contributing to the definition of the clinical severity of the syndrome.


Effects of donepezil on cortical metabolic response to activation during (18)FDG-PET in Alzheimer's disease: a double-blind cross-over trial.

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RATIONALE: Cholinergic enhancement is among the best established treatments of Alzheimer's disease (AD). The cognitive effects of treatment are thought to be mediated by improvement of neuronal transmission. Positron emission tomography using 18F-fluorodeoxyglucose (FDG-PET) by measuring cortical metabolic response to activation assesses integrity of neuronal transmission in vivo. OBJECTIVE: To determine the effects of treatment with donepezil, a centrally selective acetylcholinesterase inhibitor, on cortical metabolism in AD using 18FDG-PET. METHODS: We enrolled 23 patients, 18 of which completed the study, with mild to moderate probable AD (mini-mental status exam scores of 15-28,

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BACKGROUND.: Imaging of cerebral A(1) adenosine receptors (A(1)AR) with positron emission tomography (PET) has recently become available for neurological research. To date, it has still not been unraveled if there is a valid reference region without specific radioligand binding that may be used to improve image quantification. We conducted in vivo displacement studies in humans to elucidate this important question using the A(1)AR ligand [(18)F]CPFPX. METHODS.: Five healthy male volunteers underwent [(18)F]CPFPX bolus/infusion PET with short infusion of unlabelled CPFPX as competitor (n = 4; 0.9 to 4.0 mg) or vehicle (n = 1; control condition) after equilibrium of [(18)F]CPFPX distribution was attained. RESULTS.: Infusion of CPFPX induced a rapid displacement of [(18)F]CPFPX binding in all regions, including the cerebellum (region with lowest binding). Even at the highest competitor dose, no full displacement was reached. Displacement was dose-dependent in all regions except the cerebellum where floor effects and/or noise might have obscured dose dependency. Specific binding was estimated to account for about one third and two thirds of total equilibrium uptake in cerebellum and cortex, respectively. CONCLUSIONS.: Although the cerebellum is the region with lowest in vivo [(18)F]CPFPX binding, it is not an ideal reference region devoid of specific binding. Nevertheless, as will be discussed, the use of a reference region analysis may be a useful, non-invasive alternative analysis method in carefully selected applications.

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Positron emission tomography displacement sensitivity: predicting binding potential change for positron emission tomography tracers based on their kinetic characteristics.

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There is great interest in positron emission tomography (PET) as a noninvasive assay of fluctuations in synaptic neurotransmitter levels, but questions remain regarding the optimal choice of tracer for such a task. A mathematical method is proposed for predicting the utility of any PET tracer as a detector of changes in the concentration of an endogenous competitor via displacement of the tracer (a.k.a., its 'vulnerability' to competition). The method is based on earlier theoretical work by Endres and Carson and by the authors. A tracer-specific predictor, the PET Displacement Sensitivity (PDS), is

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calculated from compartmental model simulations of the uptake and retention of dopaminergic radiotracers in the presence of transient elevations of dopamine (DA). The PDS predicts the change in binding potential (ΔBP) for a given change in receptor occupancy because of binding by the endogenous competitor. Simulations were performed using estimates of tracer kinetic parameters derived from the literature. For D(2)/D(3) tracers, the calculated PDS indices suggest a rank order for sensitivity to displacement by DA as follows: raclopride (highest sensitivity), followed by fallypride, FESP, FLB, NMSP, and epidepride (lowest). Although the PDS takes into account the affinity constant for the tracer at the binding site, its predictive value cannot be matched by either a single equilibrium constant, or by any one rate constant of the model. Values for DeltaBP have been derived from published studies that employed comparable displacement paradigms with amphetamine and a D(2)/D(3) tracer. The values are in good agreement with the PDS-predicted rank order of sensitivity to displacement. Journal of Cerebral Blood Flow & Metabolism advance online publication, 21 June 2006; doi:10.1038/sj.jcbfm.9600359.

Cognitive dysfunction and emotional-behavioural changes in MS: the potential of positron emission tomography.

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Cognitive dysfunction and emotional-behavioural changes are symptoms with increasing clinical relevance during progression of the disease. They cannot be explained by demyelination of white matter alone but clearly indicate cortical dysfunction. Positron emission tomography (PET) provides methods to assess cortical dysfunction quantitatively by measuring cerebral glucose metabolism using the tracer (18)F-2-fluoro-2-deoxy-d-glucose (FDG). The technique has been employed to study fatigue and disease progression. Microglial activation was studied by 11C-PK-11195 PET. It was found not only in active plaques but also in degenerating fibre tracks. Other tracers offer a broad spectrum of measuring local physiological functions and pathophysiological processes, but some of them are still limited to experimental animal research.


Validation studies on the 5-hydroxy-L-[beta-11C]-tryptophan/PET method for probing the decarboxylase step in serotonin synthesis.


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The two-tissue compartment model, including irreversible trapping in the second compartment (2TCM) is used to describe the kinetics of 5-Hydroxy-L-[beta-(11)C]-tryptophan ([11]C-HTP), a radioligand used in positron emission tomography (PET) for probing the second enzymatic step in the biosynthesis of serotonin. In this study, we examined the capacity of the model to track pharmacological changes in this biological process. We also investigated the potential loss of [11]C-HTP-derived radioactivity during a PET study, since loss should be negligible not to alter quantification. Six rhesus monkeys were investigated using bolus [11]C-HTP/PET methodology before and after pharmacological intervention. The second enzymatic step in serotonin synthesis was inhibited using the aromatic L-amino acid decarboxylase inhibitor NSD1015 (10 mg/kg). The extent of [11]C-derived radioactivity loss from the brain was studied by inhibition of the enzyme responsible for formation of the tissue metabolite, monoamine oxidase A, using clorgyline (2 mg/kg). After NSD1015, the uptake of [11]C-HTP-derived radioactivity was increased in all the investigated brain regions, while the parameter used to reflect decarboxylase activity, the net accumulation rate constant (K(acc)), was decreased by 37% in the striatum, compared with baseline. Pretreatment with clorgyline did not change the brain uptake of [11]C-HTP-derived radioactivity or K(acc). This study demonstrates that the 2TCM for [11]C-HTP/PET is able to detect changes occurring during alteration of the biological process (i.e., the conversion of HTP to serotonin). Elimination of the radiotracer metabolite [11]C-HIAA from the brain may be considered negligible if the PET study is limited to 60 min. (c) 2006 Wiley-Liss, Inc.

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Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation.

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Recent data suggest that chronic tinnitus is a "phantom auditory perception" caused by maladaptive neuroplasticity and subsequent hyperactivity in an extended neuronal network including the primary auditory cortex, higher-order association areas, and parts of the limbic system. It was suggested that attenuation of this tinnitus-associated hyperactivity may offer a rational option for lasting tinnitus reduction. Here, we tested the hypothesis that tinnitus loudness can be attenuated by low-frequency repetitive transcranial magnetic stimulation (rTMS) individually navigated to cortical areas with excessive tinnitus-related activity as assessed by [(15)O]H(2)O positron-emission tomography (PET). Nine patients with chronic tinnitus underwent this combined functional imaging and rTMS study. Group analysis of the PET data showed tinnitus-related increases of regional cerebral blood flow in the left middle and inferior temporal as well as right temporoparietal cortex and posterior cingulum. Repetitive TMS was performed at 1 Hz and 120% of the motor threshold for 5, 15, and 30 min, navigated to the individual maximum of tinnitus-related cortical hyperactivity. A noncortical stimulation site with the same distance to
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the ear served as sham control. Tinnitus loudness was reduced after temporoparietal, PET-guided low-frequency rTMS. This reduction, lasting up to 30 min, was dependent on the number of stimuli applied, differed from sham stimulation, and was negatively correlated with the length of the medical history of tinnitus in our patients. These data show the feasibility and effectiveness of rTMS guided by individual functional imaging to induce a lasting, dose-dependent attenuation of tinnitus. Of note, these effects were related to stimulation of cortical association areas, not primary auditory cortex, emphasizing the crucial role of higher-order sensory processing in the pathophysiology of chronic tinnitus. Hum Brain Mapp, 2006. (c) 2006 Wiley-Liss, Inc.


Imaging of CNS myelin by positron-emission tomography.


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Promoting myelin repair is one of the most promising therapeutic avenues in the field of myelin disorders. In future clinical trials, evaluation of remyelination will require a reliable and quantifiable myelin marker to be used as a surrogate marker. To date, MRI assessment lacks specificity for evaluating the level of remyelination within the brain. Here, we describe 1,4-bis(p-aminostyryl)-2-methoxy benzene (BMB), a synthesized fluorescent molecule, that binds selectively to myelin both ex vivo and in vivo. The binding of BMB to myelin allows the detection of demyelinating lesions in an experimental autoimmune encephalitis model of demyelination and allows a mean for quantifying myelin loss in dysmyelinating mutants. In multiple sclerosis brain, different levels of BMB binding differentiated remyelination in shadow plaques from either demyelinated lesions or normal-appearing white matter. After systemic injection, BMB crosses the blood-brain barrier and binds to myelin in a dose-dependent and reversible manner. Finally, we provide evidence that (11)C-radiolabeled BMB can be used in vivo to image CNS myelin by positron-emission tomography in baboon. Our results provide a perspective for developing a brain myelin imaging technique by positron-emission tomography.


Magnetic resonance imaging and positron emission tomography findings in status epilepticus following severe hypoglycemia.

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We recently experienced a case with asymmetrical cortical abnormality on MRI with focal status epilepticus following severe hypoglycemia. The cerebral blood flow and metabolisms for oxygen and glucose were determined using positron emission tomography (PET) during focal status epilepticus following severe hypoglycemia and at the follow-up period. Prolonged seizure activity produced profound glucose hypermetabolism and mild hyperemia in the region of the presumed cortical focus of epilepsy and in structures anatomically remote from the focus, corresponding to the areas of abnormal signal intensity on the MRI. The patient remained comatose and exhibited a diffuse hypoperfusion/hypometabolism and symmetrical brain atrophy on the follow-up PET and MRI, respectively. Cytotoxic brain edema due to profound glucose metabolism without compensatory increase of the blood flow during status epilepticus may account for the brain abnormality observed on the early MRI. Simultaneous examination of the cerebral blood flow and metabolism using PET can provide useful information about the pathology in patients with status epilepticus.


Using positron emission tomography to facilitate CNS drug development.

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Positron emission tomography (PET) is a non-invasive technology of nuclear medicine that has sensitivity for tracing low picomolar concentrations of radiolabeled molecules in the human body. Radiolabeling a new drug to high specific radioactivity facilitates a detailed mapping of its distribution to crucial organs in humans after the administration of a “microdose” (< 1 microg), for which limited toxicology documentation is required. For drugs directed at the CNS, this method is particularly useful for confirming exposure to the brain. A different approach is to develop suitable radioligands for quantitative PET studies of drug binding to target proteins and subsequently to correlate receptor occupancy with pharmacodynamic responses. To follow disease progression and to monitor the outcome of new treatments, PET also facilitates longitudinal studies of biomarkers of pathophysiology such as amyloid plaque load in Alzheimer’s disease. Finally, combining genomic knowledge with PET neuroreceptor imaging is expected to facilitate the search for genetic predictors of drug response.
Necessity of a uniform start for scanning after FDG injection in brain PET study.

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The authors' goal was to show the importance of starting scanning at a uniform time after F-18 fluorodeoxyglucose injection in positron emission tomography (PET) brain study. METHOD: Fifteen healthy normal subjects underwent FDG-PET to obtain glucose metabolic images starting 60 min and 70 min after FDG injection, respectively. The two sets of images were compared in a voxel-by-voxel analysis. RESULTS: In the bilateral posterior cingulate gyrus, parietal and frontal association cortices, the FDG uptakes were larger on the 70 min scan images than on the 60 min scan images; the 60 min scans resembled Alzheimer's metabolic reduction area. Similarly the FDG uptakes were larger in the pons and vermis on the 60 min scan image than on the 70 min scan image. CONCLUSIONS: Regional FDG uptake is different depending on the time scanning starts after FDG injection, even with a 10 minute difference in start time and different scanning time may lead to misdiagnosis. It is important to standardize the start time of FDG PET after FDG injection in brain PET.


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A novel series of benzofuran derivatives as potential positron emission tomography (PET) tracers targeting amyloid plaques in Alzheimer's disease (AD) were synthesized and evaluated. The syntheses of benzofurans were successfully achieved by an intramolecular Wittig reaction between triphenylphosphonium salt and 4-nitrobenzoyl chloride. When in vitro binding studies using AD brain gray matter homogenates were carried out with a series of benzofuran derivatives, all the derivatives examined displayed high binding affinities with K(i) values in the subnanomolar range. Among these benzofuran derivatives, compound 8, 5-hydroxy-2-(4-methaminophenyl)benzofuran, showed the lowest K(i) value (0.7 nM). In vitro fluorescent labeling of AD sections with compound 8 intensely stained not only amyloid plaques, but also neurofibrillary tangles. The [(11)C]labeled compound 8, [(11)C]8, was prepared by reacting the normethyl precursor, 5-hydroxy-2-(4-aminophenyl)benzofuran, with [(11)C]methyl triflate. The [(11)C]8 displayed moderate lipophilicity (log P = 2.36), very good brain penetration (4.8%ID/g at 2 min after iv injection in mice), and rapid washout from normal brains (0.4 and 0.2%ID/g at 30 and 60 min, respectively). In addition, this PET tracer showed in vivo amyloid plaque labeling in APP transgenic mice. Taken together, the data suggest that a relatively simple benzofuran derivative, [(11)C]8, may be a useful candidate PET tracer for detecting amyloid plaques in the brains of patients with Alzheimer's disease.

Positron-emission tomography of brain regions activated by recognition of familiar music.

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BACKGROUND AND PURPOSE: We can easily recognize familiar music by listening to only one or 2 of its opening bars, but the brain regions that participate in this cognitive processing remain undetermined. We used positron-emission tomography (PET) to study changes in regional cerebral blood flow (rCBF) that occur during listening to familiar music. METHODS: We used a PET subtraction technique to elucidate the brain regions associated with the recognition of familiar melodies such as well-known nursery tunes. Nonmusicians performed 2 kinds of musical tasks; judging the familiarity of musical pieces (familiarity task) and detecting deliberately altered notes in the pieces (alteration-detecting task). RESULTS: During the familiarity task, bilateral anterior portions of bilateral temporal lobes, superior temporal regions, and parahippocampal gyri were activated. The alteration-detecting task bilaterally activated regions in the precunei, superior/inferior parietal lobules, and lateral surface of frontal lobes, which seemed to show a correlation with the analysis of music. CONCLUSION: We hypothesize that during the familiarity task, activated brain regions participate in retrieval from long-term memory and verbal and emotional processing of familiar melodies. Our results reinforced the hypothesis reported in the literature as a result of group and case studies, that temporal lobe regions participate in the recognition of familiar melodies.

Insights from recent positron emission tomographic studies of drug abuse and dependence.

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PURPOSE OF REVIEW: Recent positron emission tomographic studies demonstrate a variety of abnormalities in the brains of addicted individuals. This review aims to discuss and highlight these findings. RECENT FINDINGS: The recent findings...
are as follows: (a) the reward response to an addictive substance is associated with increased dopamine release in the striatum. (b) Activation of the orbitofrontal region is involved in the reinforcing properties of a drug. (c) Behavioral, cognitive and affective abnormalities are associated with alterations in specific brain networks and regions (e.g., prefrontal cortices) in drug abusers. (d) Personality traits may play a role in the susceptibility to addiction and the brain's responses to drugs. (e) Sex-differences exist for cue-induced craving. (f) Several studies have confirmed decreased D2 receptors in drug users, which is associated with increased salience to drug cues. (g) Serotoninergic transporters are decreased in the current users of 3,4-methylene-deoxy-methamphetamine but found normal in the past users of 3,4-methylene-deoxy-methamphetamine.

SUMMARY: Abnormalities in the dopaminergic, opioid, and serotonergic systems in drug abusers are seen in positron emission tomography scans. Decreased D2 receptor densities in drug users, whether premorbid or the consequence of substance misuse, imply a source of the susceptibility to relapse of this population. Insights from these studies could lead to better treatment approaches targeting specific neurotransmitter systems.
18F-fluorodeoxyglucose hypometabolism in cerebellar tonsil and flocculus in downbeat nystagmus.

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A patient with downbeat nystagmus was examined by F-fluorodeoxyglucose-positron emission tomography once while off and twice while on successful treatment with 4-aminopyridine. All positron emission tomography scans of the patient showed a reduced cerebral glucose metabolism bilaterally in the region of the cerebellar tonsil and flocculus/paraflocculus when compared with a normal database of the whole brain. An additional region-of-interest analysis revealed that 4-aminopyridine treatment lessened the hypometabolism. This finding supports the hypothesis that the cerebellar tonsil and (para-) flocculus play a crucial role in downbeat nystagmus. The hypometabolism might reflect reduced inhibition or even disinhibition of the circuits to the vestibular nuclei, thus causing downbeat nystagmus. The reduced hypometabolism during treatment probably indicates an improvement of the cerebellar inhibition.
Kimura's disease with generalized lymphadenopathy demonstrated by positron emission tomography scan.

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Kimura's disease is a chronic inflammatory disorder that occurs mainly in Asian patients. Most imaging studies focus on the loco-regional involvement of this disorder. Images of the whole body fluorine-18 fluorodeoxyglucose positron emission tomography (18F-FDG PET) scan have not been reported in the literature before. The possibility of lymphoid clonality is also discussed frequently despite its clinically benign course. We present a patient of Kimura's disease initially assessed by whole body 18F-FDG PET study and proved by pathologic findings. 18F-FDG-PET scan showed diffusely intense uptake in the neck, axillary, pelvic and inguinal nodal regions bilaterally, as well as in the mediastinal, celiac region. The flow cytometric analysis of lymph node tissue confirmed the absence of clonality. The image of 18F-FDG-PET in Kimura's disease can closely resemble that seen in neoplastic disorders such as lymphoma or metastatic lymphadenopathy. It should be taken into consideration as a differential diagnosis for a generalized lymphadenopathy.

Optimization algorithms and weighting factors for analysis of dynamic PET studies.

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Positron emission tomography (PET) pharmacokinetic analysis involves fitting of measured PET data to a PET pharmacokinetic model. The fitted parameters may, however, suffer from bias or be unrealistic, especially in the case of noisy data. There are many optimization algorithms, each having different characteristics. The purpose of the present study was to evaluate (1) the performance of different optimization algorithms and (2) the effects of using incorrect weighting factors during optimization in terms of both accuracy and reproducibility of fitted PET pharmacokinetic parameters. In this study, the performance of commonly used optimization algorithms (i.e. interior-reflective Newton methods) and a simulated annealing (SA) method was evaluated. This SA algorithm, known as basin hopping, was modified for the present application. In addition, optimization was performed using various weighting factors. Algorithms and effects of using incorrect weighting factors were studied using both simulated and clinical time-activity curves (TACs). Input data, taken from [(15)O]H(2)O, [(11)C]flumazenil and [(11)C](R)-PK11195 studies, were used to simulate time-activity curves at various variance levels (0-15% COV). Clinical evaluation was based on studies with the same three tracers. SA was able to produce accurate results without the need for selecting appropriate starting values for (kinetic) parameters, in contrast to the interior-reflective Newton method. The latter gave biased results unless it was modified to allow for a range of starting values for the different parameters. For patient studies, where large variability is expected, both SA and the extended Newton method provided accurate results. Simulations and clinical assessment showed similar results for the evaluation of different weighting models in that small to intermediate mismatches between data variance and weighting factors did not significantly affect the outcome of the fits. Large errors were observed only when the mismatch between weighting model and data variance was large. It is concluded that selection of specific optimization algorithms and weighting factors can have a large effect on the accuracy and precision of PET pharmacokinetic analysis. Apart from carefully selecting appropriate algorithms and variance models, further improvement in accuracy might be obtained by using noise reducing strategies, such as wavelet filtering, provided that these methods do not introduce significant bias.

Synthesis and evaluation of [(18)f] labeled pyrimidine nucleosides for positron emission tomography imaging of herpes simplex virus 1 thymidine kinase gene expression.

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Synthesis of three novel 2'-deoxy-2'-(18)F]fluoro-1-beta-d-arabinofuranosyluracil derivatives [(18)F]FPAU, [(18)F]FBrVAU, and [(18)F]FTMAU is reported. The compounds were synthesized by coupling of 1-bromo-2-deoxy-2-fluoro sugars with corresponding silylated uracil derivatives. In vitro cell uptake indicated that all three compounds are taken up selectively in RG2TK+ cells with negligible uptake in RG2 cells. The results indicate that [(18)F]FBrVAU and [(18)F]FTMAU have better uptake profiles in comparison to [(18)F]FPAU and have potential as PET probes for imaging HSV1-tk gene expression.
PET-Miscellaneous

Masked Prosthetic Graft to Sigmoid Colon Fistula Diagnosed by 18-fluorodeoxyglucose Positron Emission Tomography.


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The diagnosis of low grade prosthetic graft infection or aorto-enteric fistula is difficult using conventional radiographic imaging modalities. We report a case of aorto-enteric fistula to the sigmoid colon diagnosed by the new technique of 18-fluorodeoxyglucose positron emission tomography.

Disease activity and (18)F-FDG uptake in organising pneumonia: semi-quantitative evaluation using computed tomography and positron emission tomography.

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Purpose: The present study was conducted to evaluate whether (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) in combination with computed tomography (CT) reflects disease activity in patients with organising pneumonia.

Methods: Eighty-eight subjects who were normal (n=66) or who had proven organising pneumonia (n=22) underwent FDG-PET and CT imaging. The subjects included 55 men and 33 women, ranging in age from 24 to 63 years (mean 47 years). PET and CT data sets were digitally fused using a conformational PET/CT fusion algorithm. All scans were evaluated independently by two chest radiologists who were unaware of other clinical data. The visual score, maximal and mean standardised uptake value (SUV), and maximal and mean lesion-to-normal tissue ratio (LNR) were calculated. The imaging results were compared with the laboratory and pulmonary function test results. The inflammatory cells in the lesions were quantified immunohistochemically.

Results: The visual score, maximal and mean SUV, and maximal and mean LNR of the patients with organising pneumonia were significantly higher than those of the normal subjects. The patients with air-space consolidation had a significantly higher SUV than those without air-space consolidation (mean+/-SD 3.08+/-0.39 vs 2.35+/-0.56; p<0.05). The number of CD45(+) cells was positively correlated with the maximal SUV (r=0.632, p<0.01) and the maximal LNR (r=0.453, p<0.05). The number of CD8(+) T lymphocytes also showed positive correlations with the maximal SUV (r=0.540, p<0.01) and the maximal LNR (r=0.547, p<0.01).

Conclusion: Patients with organising pneumonia have an enhanced FDG accumulation which reflects the degree of disease activity.

The diagnosis of ectopic focal hyperinsulinism of infancy with [18F]-dopa positron emission tomography.

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BACKGROUND: Congenital hyperinsulinism (CHI) is a cause of severe hypoglycemia in the neonatal and infancy period. Histologically, there are two subtypes with diffuse and focal disease. The preoperatative differentiation of these two forms is very important because the surgical management is radically different. The focal form of the disease can be cured if the focal lesion can be localized accurately and completely resected with surgery. AIM: We report the case of a child who underwent three pancreatectomies with a choledochoduodenostomy and a cholecystectomy but continued to have severe hyperinsulinemic hypoglycemia. METHODS/RESULTS: Radiological investigations including imaging with (18)fluoro-L-Dopa positron emission tomography scan showed a clear focus of increased (18)F-fluoro-L-Dopa uptake in the vicinity of the former head of the pancreas. On the magnetic resonance imaging scan, this focal uptake appeared to localize adjacent or next to duodenum (in the wall or cavity of the duodenum). CONCLUSIONS: This unique case highlights the importance of correctly localizing and completely resecting the focal lesion in patients with CHI. (18)Fluoro-L-Dopa positron emission tomography scan can identify ectopic focal lesions in patients with CHI.

Positron emission tomography.

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The developments in positron emission tomography (PET) are reviewed with an emphasis on instrumentation for clinical PET imaging. After a brief summary of positron imaging before the advent of computed tomography, various improvements are highlighted including the move from PET scanners with septa to fully 3D scanners, changes in the preferred scintillators, efforts to improve the energy discrimination, and improvements in attenuation correction. Time-of-flight PET imaging is given special attention due to the recent revival of this technique, which promises significant improvement. Besides technical instrumentation efforts, other factors which influenced the acceptance of clinical PET are also discussed.
Post-transplant lymphoproliferative disease (PTLD) is a serious and potentially life-threatening complication after solid organ transplantation. Here, we report our first experience with the use of PET/CT (positron emission tomography combined with computed tomogram) for the management of patients with PTLD after liver transplantation. Four patients with histologically proven PTLD were analyzed. Conventional work-up included physical examination and head-to-pelvis CT. PET/CT was used in one patient for initial staging and in all patients for follow-up. PET/CT positive findings underwent biopsy. Information provided by PET/CT resulted in a change of medical management in three of the four patients. Conventional work-up missed residual disease after surgery in one and failed to detect a tumor relapse in another patient. However, one patient disclosed a false positive PET/CT finding in the lungs. In conclusion, PET/CT may be a useful tool for staging and therapy monitoring of PTLD after liver transplantation.

Heresi GA, Mazzone PJ, Stoller JK.

Impact of positron emission tomography on clinical decision making.

Heresi GA, Mazzone PJ, Stoller JK.


F-18 FDG whole-body PET for the assessment of disease activity in patients with rheumatoid arthritis.


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PURPOSE OF REPORT: F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) can be used to image synovitis in patients with rheumatoid arthritis (RA). The aim of this study was to evaluate if a simple scoring system based on visual assessment of FDG joint uptake correlates with the clinical assessment of patients with RA undergoing antiinflammatory treatment. MATERIALS AND METHODS: Seven patients with active RA underwent whole-body FDG PET and clinical assessment before and after treatment with the antitumor necrosis factor alpha antibody (infliximab). A PET total joint score, ie, the sum of all scores based on FDG uptake intensity between zero and 4 in 28 joints, was correlated with a total joint score based on the clinical disease activity in the same joints using a Spearman rank correlation. RESULTS: The PET based total joint score was similarly high before onset as was the clinical total joint score. The decrease of FDG joint uptake in the follow-up PET scans correlated significantly with the clinical assessment. Additionally, synovial FDG uptake was found in extraarticular sites such as tendon sheaths and bursae. CONCLUSIONS: Visual assessment of FDG uptake shows a significant correlation with clinical evaluation of disease activity in patients with RA undergoing antiinflammatory treatment.


Fourier-based reconstruction for fully 3-D PET: optimization of interpolation parameters.

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Fourier-based approaches for three-dimensional (3-D) reconstruction are based on the relationship between the 3-D Fourier transform (FT) of the volume and the two-dimensional (2-D) FT of a parallel-ray projection of the volume. The critical step in the Fourier-based methods is the estimation of the samples of the 3-D transform of the image from the samples of the 2-D transforms of the projections on the planes through the origin of Fourier space, and vice versa for forward-projection (reprojection). The Fourier-based approaches have the potential for very fast reconstruction, but their straightforward implementation might lead to unsatisfactory results if careful attention is not paid to interpolation and weighting functions. In our previous work, we have investigated optimal interpolation parameters for the Fourier-based forward and back-projectors for iterative image reconstruction. The optimized interpolation kernels were shown to provide excellent quality comparable to the ideal sinc interpolator. This work presents an optimization of interpolation parameters of the 3-D direct Fourier method with Fourier reprojeciton (3D-FRP) for fully 3-D positron emission tomography (PET) data with incomplete oblique projections. The reprojection step is needed for the estimation (from an initial image) of the missing portions of the oblique data. In the 3D-FRP implementation, we use the gridding interpolation strategy, combined with proper weighting approaches in the transform and image domains. We have found that while the 3-D reprojection step requires similar optimal interpolation parameters as found in our previous studies on Fourier-based iterative approaches, the optimal interpolation parameters for the main 3D-FRP reconstruction stage are quite different. Our experimental results confirm that for the optimal interpolation parameters a very good image accuracy can be achieved even without any extra spectral oversampling, which is a common practice to decrease errors caused by interpolation in Fourier reconstruction.
PET-Miscellaneous

Modeling and incorporation of system response functions in 3-D whole body PET.

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Appropriate application of spatially variant system models can correct for degraded resolution response and mispositioning errors. This paper explores the detector blurring component of the system model for a whole body positron emission tomography (PET) system and extends this factor into a more general system response function to account for other system effects including the influence of Fourier rebinning (FORE). We model the system response function as a three-dimensional (3-D) function that blurs in the radial and axial dimension and is spatially variant in radial location. This function is derived from Monte Carlo simulations and incorporates inter-crystal scatter, crystal penetration, and the blurring due to the FORE algorithm. The improved system model is applied in a modified ordered subsets expectation maximization (OSEM) algorithm to reconstruct images from rebinned, fully 3-D PET data. The proposed method effectively removes the spatial variance in the resolution response, as shown in simulations of point sources. Furthermore, simulation and measured studies show the proposed method improves quantitative accuracy with a reduction in tumor bias compared to conventional OSEM on the order of 10%-30% depending on tumor size and smoothing parameter.

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[Positron emission tomography: current use in internal medicine and future developments.]

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PURPOSE: Fluorodeoxyglucose positron emission tomography (FDG-PET) is a promising imaging technique that has already proven effective in modifying patient care in oncology. Fluorodeoxyglucose still remains the main radiopharmaceutical agent routinely used for PET imaging. A growing interest has recently lead to broaden PET research on benign disorders. The field of inflammatory or immune diseases and globally the field of internal medicine could also be impacted by FDG-PET. MAIN POINTS: Great vessels vasculitides and fever of unknown origin have both been studied by several teams and could become indications for PET. In addition, current indications now extend to paraneoplastic syndromes. It is thus possible to foresee that the clinical applications for PET will continue to expand in these patients. PERSPECTIVES AND PROJECTS: In the future, inflammatory arthritis, chronic inflammatory bowel diseases, sytemic erythematous lupus, histiocytosis, or pulmonary and retroperitoneal fibrosis might benefit from PET even if, available data remains scarce to this day. Although PET will probably alter the landscape of patient management in internal medicine in the near future, additional clinical research is still needed to ascertain the exact role of PET.


Quantifying pulmonary inflammation in cystic fibrosis with positron emission tomography.

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RATIONALE: Although infection contributes to morbidity in patients with cystic fibrosis (CF), the host inflammatory response is also an important cause of progressive pulmonary function deterioration. Quantifying the inflammatory burden in these patients is challenging and often requires invasive procedures. Positron emission tomographic imaging with [18F]fluorodeoxyglucose ([18FDG]) could be used as a noninvasive alternative to quantify lung inflammation. OBJECTIVE: To determine the relationships among lung [18F]FDG uptake, bronchoalveolar lavage (BAL) neutrophil concentrations, and pulmonary function in patients with CF. METHODS: Twenty patients and seven healthy volunteers were studied. A subset of seven patients also consented to undergo BAL. The uptake of [18F]FDG by the lungs was measured as the net influx rate constant K_i. Patients were stratified by rate of decline in pulmonary function into stable, intermediate, and rapidly declining groups. K_i was compared among groups and was correlated against neutrophil concentrations in BAL fluid. RESULTS: K_i was significantly elevated (p<0.05) among patients with CF as a whole compared with healthy control subjects (0.0015+/-0.0009 versus 0.0007+/-0.0002 ml blood/ml lung/min) but especially in patients with rapidly declining pulmonary function (0.0022+/-0.0011 ml blood/ml lung/min). K_i correlated positively with the number of neutrophils present in BAL fluid. CONCLUSION: Imaging with [18F]fluorodeoxyglucose and positron emission tomography can be used to assess inflammatory burden in patients with CF. Elevations in K_i may be able to identify patients with more aggressive disease and may be useful in monitoring changes in inflammatory burden in response to novel treatments.
PET energy-based scatter estimation and image reconstruction with energy-dependent corrections.

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In this paper we propose a comprehensive energy-based scatter correction approach for positron emission tomography (PET). We take advantage of the marked difference between the energy spectra of the unscattered and scattered photons, and use the detailed energy information that comes with the list-mode data for the estimation of the scattered events distribution in the data space. Also, inside the maximum-likelihood expectation maximization (ML-EM) image reconstruction algorithm, we introduce energy-dependent factors that individualize the correction terms for each event, given its position and energy information. The central piece of our approach is the two-dimensional detector energy response model represented as a linear combination of four components, each one representing a particular state a PET event can be found in: both photons unscattered, the second scattered while the first not, the first photon scattered while the second not and both photons scattered. For a set of events collected in the vicinity of a point in the projection space, the coefficient of each component is determined by applying a statistical estimator. As a result we obtain the number of scattered events that are in the given set. The model also gives us the variation of scatter fraction with the photon pair energies for that particular position in the data space. A simulation study that demonstrates the proposed methods is presented.


Positron emission tomography imaging of regional lung function.

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Regional pulmonary perfusion and ventilation can be assessed by imaging, with positron emission tomography (PET), the pulmonary kinetics of [13N]nitrogen (13N2). Because of its low solubility in blood and tissues, 13N2 infused intravenously in saline solution evolves into the alveolar airspace at first pass, where it accumulates in proportion to regional perfusion during a short apnea. In contrast, infused 13N2 is not retained in non-aerated regions, which do not exchange gas. Robust estimates of regional perfusion and shunt are obtained by modeling the pulmonary kinetics of 13N2 infused as a bolus during a short apnea. Regional ventilation is measured by modeling the washout of 13N2 after breathing is resumed. Regional gas content and dead space ventilation can be measured with inhalation of 13N2. Application of this novel functional imaging technique can further the understanding of the pathophysiology of a variety of pulmonary processes. This review briefly describes the methodological aspects of PET imaging of regional perfusion and ventilation and then focuses on insights in the pathophysiology of acute lung injury and asthma that have been gained by imaging the pulmonary kinetics of 13N2 with PET.

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Imaging of infection and inflammation with 18F-FDG-labeled leukocytes.

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Conventional scintigraphic imaging with (67)Ga citrate and in vitro labeled leukocytes is routinely used to evaluate infectious and inflammatory conditions. Recent studies suggest that positron emission tomography (PET) with [(18)F]fluorodeoxyglucose (FDG) also may be useful in this setting. Both (67)Ga citrate and [(18)F]FDG are highly sensitive tracers, but their specificity for detecting infection is lower than that of in vitro labeled leukocytes, which is the radionuclide gold standard for imaging most infections. PET has several advantages over conventional scintigraphic techniques, including higher spatial resolution and faster imaging times. In vitro [(18)F]FDG labeled leukocytes represent an initial attempt to develop an infection-specific, positron-emitting tracer. The experience to date with PET imaging of [(18)F]FDG labeled leukocytes is reviewed in this article.
(18)F Fluorodeoxyglucose-positron emission tomography (FDG-PET) has become an encouraging imaging modality in musculoskeletal infection. This application has an incremental value in the assessment of both acute and chronic infection and has shown to be more accurate in detecting chronic osteomyelitis than conventional radionuclide imaging. Although FDG-PET has the potential to replace conventional scintigraphy completely depends on a number of factors, including cost and availability. Conventional radionuclide studies have represented imaging methods of choice in the diagnosis of implant-associated infection in patients with trauma so far. However, nonspecific tissue uptake of imaging agents and limited spatial resolution restrict their usefulness. Magnetic resonance imaging (MRI) and computed tomography (CT) image quality is degraded in the presence of metallic implants due to susceptibility and beam-hardening artifacts, respectively. Although its role is still evolving, FDG-PET imaging will have increased importance in patients with metallic implants used for trauma surgery because FDG uptake is not hampered by metallic artifacts. In contrast to patients with metallic implants, PET may not be as useful in the diagnosis of infection in patients with failed total joint replacements. In this situation, combined 111Indium-labeled leucocyte/(99m)Tc-sulfur colloid marrow imaging still remains the gold standard. This article reviews the currently available literature on FDG-PET and PET/CT in the diagnosis of musculoskeletal infection.

**OBJECTIVES:** To evaluate the usefulness of integrated positron emission tomography and computed tomography (PET/CT) in staging mycosis fungoides (MF) and Sezary syndrome and to correlate PET/CT data with histopathologic diagnosis of lymph nodes (LNs). DESIGN: A single-center, prospective cohort analysis. SETTING: Academic referral center for cutaneous lymphoma. PATIENTS: Thirteen patients with MF and SS at risk for secondary LN involvement. Interventions Patients were clinically evaluated based on general physical examination, total body skin examination, and laboratory screening. They underwent integrated PET/CT followed by excisional biopsy of LNs. MAIN OUTCOME MEASURES: We used PET/CT to assess LN size and metabolic activity. Enlarged LNs were defined as axillary or inguinal LNs with a short period of time available for nuclear imaging when there is no magnetic field present. This work focuses upon the effect of the field-cycled MRI upon the nuclear image due to the added material providing additional attenuation of the PET signal, and additional nuclei for scatter. These effects are studied using a Monte Carlo simulation based upon the GEANT libraries. Attenuation effects are shown to be significant, approximately 6% for the RF shield and coil and approximately 24% for the gradients. No significant effect is seen in image quality due to the scattering of the gammas. With these levels of attenuation it is concluded that open gradient coils and shim oils are required around the imaging volume.

**Integrating PET and MRI for disease activity:**

**[18FDG PET: a new criterion for disease activity in Takayasu arteritis]**

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INTRODUCTION: Takayasu arteritis (TA) is an inflammatory arteritis affecting large vessels, predominantly the aorta, its main branches, and the pulmonary arteries. Up to now, arteriography was considered as the "gold standard". But others exams are emerging in the management of TA: vascular ultrasound, angio-scanner, magnetic resonance imaging and 18FDG positron emission tomography (18FDG PET). Such investigations allow a study of the lumen but also of the arterial walls. However, at the time, no biological or radiological test is able to determine the activity of TA. 18FDG PET could be effective to estimate the disease activity. EXEGESIS: We report the case of a young woman for whom 18FDG PET permit to assert a relapse of TA. CONCLUSION: 18FDG PET could be effective to estimate the disease activity.

**Simulation of scattering and attenuation of 511 keV photons in a combined PET/field-cycled MRI system.**

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Mixing the imaging modalities of positron emission tomography (PET) and magnetic resonance imaging (MRI) will offer the best soft tissue contrast (MRI) with information about metabolic function (PET). The high magnetic field environment of an MRI system makes the detection of annihilation photons difficult, as the response of standard photo-multiplier tubes is compromised. An approach using field-cycled MRI is discussed here, as field-cycled MRI makes it possible to have long periods of time available for nuclear imaging when there is no magnetic field present. This work focuses upon the effect of the field-cycled MRI upon the nuclear image due to the added material providing additional attenuation of the PET signal, and additional nuclei for scatter. These effects are studied using a Monte Carlo simulation based upon the GEANT libraries. Attenuation effects are shown to be significant, approximately 6% for the RF shield and coil and approximately 24% for the gradients. No significant effect is seen in image quality due to the scattering of the gammas. With these levels of attenuation it is concluded that open gradient coils and shim coils are required around the imaging volume.

**Staging accuracy in mycosis fungoides and sezary syndrome using integrated positron emission tomography and computed tomography.**


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OBJECTIVES: To evaluate the usefulness of integrated positron emission tomography and computed tomography (PET/CT) in staging mycosis fungoides (MF) and Sezary syndrome and to correlate PET/CT data with histopathologic diagnosis of lymph nodes (LNs). DESIGN: A single-center, prospective cohort analysis. SETTING: Academic referral center for cutaneous lymphoma. PATIENTS: Thirteen patients with MF and SS at risk for secondary LN involvement. Interventions Patients were clinically evaluated based on general physical examination, total body skin examination, and laboratory screening. They underwent integrated PET/CT followed by excisional biopsy of LNs. MAIN OUTCOME MEASURES: We used PET/CT to assess LN size and metabolic activity. Enlarged LNs were defined as axillary or inguinal LNs with a short period of time available for nuclear imaging when there is no magnetic field present. This work focuses upon the effect of the field-cycled MRI upon the nuclear image due to the added material providing additional attenuation of the PET signal, and additional nuclei for scatter. These effects are studied using a Monte Carlo simulation based upon the GEANT libraries. Attenuation effects are shown to be significant, approximately 6% for the RF shield and coil and approximately 24% for the gradients. No significant effect is seen in image quality due to the scattering of the gammas. With these levels of attenuation it is concluded that open gradient coils and shim coils are required around the imaging volume.
axis 1.5 cm or larger; or cervical LN, with a short axis 1.0 cm or larger. We classified LN pathologic results according to National Cancer Institute (LN1-4) and World Health Organization (WHO 1-3) criteria. We quantified PET activity using standardized uptake value (SUV) and correlated with LN grade. RESULTS: Based on CT size criteria alone, only 5 patients had enlarged LNs, whereas PET revealed hypermetabolic LNs in all 13 patients. Six patients had LN1-3, and 7 had effacement of LN architecture by lymphoma cells (LN4). Of the 7 patients with LN4 nodes, 4 had SS, and 3 had tumorous MF. Two patients with LN4 nodes had inguinal LNs smaller than 1.5 cm and would have been assigned an N0 classification without the use of integrated PET/CT. Correlation of SUV with LN grade revealed that LN1-3 nodes were associated with a mean SUV of 2.7 (median SUV, 2.2; range, 2.0-4.7) and LN4 nodes were associated with a mean SUV of 5.4 (median SUV, 3.9; range, 2.1-11.8). Patients with large cell transformation had the highest SUVs. CONCLUSIONS: For staging MF and SS, PET/CT was more sensitive in detecting LN involved by lymphoma compared with CT data alone and thus may provide more accurate staging and prognostic information. The intensity of PET activity correlated with histologic LN grade.

Giant cell arteritis revealed by positron emission tomography.

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Diffuse bowel fluorodeoxyglucose uptake on positron emission tomography scan following allogeneic stem cell transplant.

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FDG-PET imaging of pulmonary inflammation in healthy volunteers after airway instillation of endotoxin.

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Recent studies indicate that a focal, limited, inflammatory response can be safely elicited after direct bronchial instillation of small doses of endotoxin into a single lung segment. Because the radiotracer [18F]fluorodeoxyglucose ([18F]FDG) is taken up at accelerated rates within inflamed tissues, we hypothesized that we could detect and quantify this regional inflammatory response with positron emission tomography (PET). We imaged 18 normal volunteers in a dose-escalation study with 3 endotoxin dosing groups (n = 6 in each group): 1 ng/kg, 2 ng/kg, and 4 ng/kg. Endotoxin was instilled by bronchoscopy into a segment of the right middle lobe, with imaging performed approximately 24 h later, followed by bronchoalveolar lavage (BAL). A "subtraction imaging analysis" was performed in the highest dose cohort to identify the area of inflammation, using the preendotoxin scan as a baseline. BAL neutrophil counts were significantly higher in the highest dose group compared with the other two groups (1,413 +/- 625 vs. 511 +/- 396 and 395 +/- 400 cells/mm3; P < 0.05). Autoradiography performed on cells harvested by BAL showed specific [3H]deoxyglucose ([3H]DG) uptake limited to neutrophils. In vitro [3H]DG uptake in BAL neutrophils in the 4 ng/kg dose group (but not in the 2 ng/kg group) was statistically greater than in peripheral blood neutrophils obtained before endotoxin instillation. The rate of [18F]FDG uptake was greatest in the 4 ng/kg group, with a consistent, statistically significant increase in the rate of uptake after endotoxin instillation compared with baseline. We conclude that the inflammatory response to low-dose endotoxin in a single lung segment can be visualized and quantified by imaging with FDG-PET.