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Radiology. 2011 Sep;260(3):689-98.

Detection of Hemodynamically Significant Coronary Artery Stenosis: Incremental Diagnostic Value of Dynamic CT-based Myocardial Perfusion Imaging.

Bamberg F, Becker A, Schwarz F, Marcus RP, Greif M, von Ziegler F, Blankstein R, Hoffmann U, Sommer WH, Hoffmann VS, Johnson TR, Becker HC, Wintersperger BJ, Reiser MF, Nikolaou K.

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Purpose: To determine the feasibility of computed tomography (CT)-based dynamic myocardial perfusion imaging for the detection of hemodynamically significant coronary artery stenosis, as defined with fractional flow reserve (FFR). Materials and Methods: Institutional review board approval and informed patient consent were obtained before patient enrollment in the study. The study was HIPAA compliant. Subjects who were suspected of having or were known to have coronary artery disease underwent electrocardiographically triggered dynamic stress myocardial perfusion imaging. FFR measurement was performed within all main coronary arteries with a luminal narrowing of 50%-85%. Estimated myocardial blood flow (MBF) was derived from CT images by using a model-based parametric deconvolution method for 16 myocardial segments and was related to hemodynamically significant coronary artery stenosis with an FFR of 0.75 or less in a blinded fashion. Conventional measures of diagnostic accuracy were derived, and discriminatory power analysis was performed by using logistic regression analysis. Results: Of 36 enrolled subjects, 33 (mean age, 68.1 years \pm 10 [standard deviation]; 25 [76%] men, eight [24%] women) completed the study protocol. An MBF cut point of 75 mL/100 mL/min provided the highest discriminatory power (C statistic, 0.707; $P < .001$). While the diagnostic accuracy of CT for the detection of anatomically significant coronary artery stenosis ($>50\%$) was high, it was low for the detection of hemodynamically significant stenosis (positive predictive value [PPV] per coronary segment, 49%; 95% confidence interval [CI]: 36%, 60%). With use of estimated MBF to reclassify lesions depicted with CT angiography, 30 of 70 (43%) coronary lesions were graded as not hemodynamically significant, which significantly increased PPV to 78% (95% CI: 61%, 89%; $P = .02$). The presence of a coronary artery stenosis with a corresponding MBF less than 75 mL/100 mL/min had a high risk for hemodynamic significance (odds ratio, 86.9; 95% CI: 17.6, 430.4). Conclusion: Dynamic CT-based stress myocardial perfusion imaging may allow detection of hemodynamically significant coronary artery stenosis.

Am Heart J. 2011 Aug;162(2):283-290.e2.

Quality of acute myocardial infarction care and outcomes in 33,997 patients aged 80 years or older: Findings from Get With The Guidelines-Coronary Artery Disease (GWTG-CAD).

Medina HM, Cannon CP, Zhao X, Hernandez AF, Bhatt DL, Peterson ED, Liang L, Fonarow GC.

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To determine the adherence to national guidelines and in-hospital mortality of older patients with acute myocardial infarction (AMI) using a national database. Prior studies have demonstrated that older patients are less likely to receive evidence-based therapies. Using data from the GWTG-CAD, we examined care and in-hospital outcomes among AMI patients treated at 416 US centers from 2000 to 2009. Evidence-based medical therapy, other quality measures, and in-hospital post-AMI mortality were analyzed. A total of 156,677 patients were included in the study; 21.7% ($n = 33,997$) were aged ≥ 80 years, 33.0% ($n = 51,773$) 65 to 79 years, and 45.3% ($n = 70,907$) 18 to 64 years. Older patients had higher prevalence of comorbidities compared to younger patients. Overall, compliance with evidence-based medical treatment upon admission and discharge was high, but age-related differences in care were seen for most measures. After multivariate adjustment, the mortality of the patients aged ≥ 80 years was substantially higher compared to the youngest cohort (adjusted OR 3.4, 95% CI 3.2-3.8, $P < .0001$). There were substantial improvements in AMI quality measures over time in each age group. Among AMI patients aged ≥ 80 years, the use of evidence-based therapies was high and significant improvements over time have been observed in a national quality improvement program. Nevertheless, there remain important age-related gaps in care and outcomes, suggesting opportunities exist to improve prognosis in this high-risk population.

Nucl Med Biol. 2011 Aug 8. [Epub ahead of print]

Reduced CGP12177 binding to cardiac β -adrenoceptors in hyperglycemic high-fat-diet-fed, streptozotocin-induced diabetic rats.

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Abnormal sympathetic nervous system and β -adrenoceptor (β -AR) signaling is associated with diabetes. [(3)H]CGP12177 is a nonselective β -AR antagonist that can be labeled with carbon-11 for positron emission tomography. The aim of this study was to examine the suitability of this tracer for evaluation of altered β -AR expression in diabetic rat hearts. Ex vivo biodistribution with [(3)H]CGP12177 was carried out in normal

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Sprague-Dawley rats for evaluation of specific binding and response to continuous β -AR stimulation by isoproterenol. In a separate group, high-fat-diet feeding imparted insulin resistance and a single intraperitoneal injection of streptozotocin (STZ) or vehicle evoked hyperglycemia (blood glucose >11 mM). [(3)H]CGP12177 biodistribution was assessed at 2 and 8 weeks post-STZ to measure β -AR binding in heart, 30 min following tracer injection. Western blotting of β -AR subtypes was completed in parallel. Infusion of isoproterenol over 14 days did not affect cardiac binding of [(3)H]CGP12177. Approximately half of rats treated with STZ exhibited sustained hyperglycemia and progressive hypoinsulinemia. Myocardial [(3)H]CGP12177 specific binding was unchanged at 2 weeks post-STZ but significantly reduced by 30%-40% at 8 weeks in hyperglycemic but not euglycemic STZ-treated rats compared with vehicle-treated controls. Western blots supported a significant decrease in $\beta(1)$ -AR in hyperglycemic rats. Reduced cardiac [(3)H]CGP12177 specific binding in the presence of sustained hyperglycemia corresponds to a decrease in relative $\beta(1)$ -AR expression. These data indirectly support the use of [(11)C]CGP12177 for assessment of cardiac dysfunction in diabetes.

J Am Coll Cardiol. 2011 Aug 9;58(7):740-8.

Impaired myocardial flow reserve on rubidium-82 positron emission tomography imaging predicts adverse outcomes in patients assessed for myocardial ischemia.

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We evaluated the prognostic value of myocardial flow reserve (MFR) using rubidium-82 ((82)Rb) positron emission tomography (PET) in patients assessed for ischemia. The clinical value of MFR quantification using (82)Rb PET beyond relative myocardial perfusion imaging remains uncertain. We prospectively enrolled 704 consecutive patients; 677 (96%) completed follow-up (median 387 days [interquartile range: 375 to 416 days]). Patients were divided into 4 groups: I, normal summed stress score (SSS) (<4) and normal myocardial flow reserve (MFR) (>2); II, normal SSS and MFR <2; III, SSS \geq 4 and MFR \geq 2; IV, SSS \geq 4 and MFR <2. For patients with a normal SSS and those with an abnormal SSS, there were significant differences in outcomes for hard events (cardiac death and myocardial infarction) between patients with MFR \geq 2 and those with MFR <2 (I: 1.3% vs. II: 2% [p = 0.029]; III: 1.1% vs. IV: 11.4% [p = 0.05]) and for major adverse cardiac events (MACE) (p = 0.003 and p < 0.001, respectively). In the adjusted Cox model, MFR was an independent predictor of hard events (hazard ratio: 3.3; 95% confidence interval: 1.1 to 9.5; p = 0.029) and MACE (hazard ratio: 2.4, 95% confidence interval: 1.4 to 4.4, p = 0.003). The incremental prognostic value of the MFR over the SSS was demonstrated by comparing the adjusted SSS model with and without the MFR for hard events (p = 0.0197) and MACE (p = 0.002). MFR quantified using (82)Rb PET predicts hard cardiac events and MACE independent of the SSS and other parameters. Routine assessment of (82)Rb PET-quantified MFR could improve risk stratification for patients being investigated for ischemia.

Curr Opin Cardiol. 2011 Sep;26(5):370-8.

Radionuclide cardiac stress testing.

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To briefly review the field of radionuclide stress imaging, including recent technologic advances and clinical applications.

ECG gating and attenuation correction help increase specificity and accuracy of myocardial single-photon emission computed tomography (SPECT) imaging. Furthermore, advances in camera hardware and software enable more rapid image acquisition and/or radiation dose reduction. Position emission tomography (PET) and hybrid imaging with computer tomography (CT) are emerging technologies which provide improved image resolution and complementary anatomical data. Nuclear cardiology also demonstrates a wide variety of prognostic applications for a diverse group of patient subgroups. More judicious use of SPECT technology using application of the recently updated appropriateness criteria is encouraged. Radionuclide stress imaging provides essential clinical information and has clear impact on patient assessment and management.

Atherosclerosis. 2011 Jul 6. [Epub ahead of print]

Influence of pericoronary adipose tissue on local coronary atherosclerosis as assessed by a novel MDCT volumetric method.

Maurovich-Horvat P, Kallianos K, Engel LC, Szymonifka J, Fox CS, Hoffmann U, Truong QA.

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Pericoronary adipose tissue (PCAT) may create a pro-inflammatory state, contributing to the development of coronary artery disease (CAD). We sought to evaluate the feasibility of a novel volumetric PCAT quantification method using a novel threshold based computed tomography approach. In addition we determined the relation between PCAT volumes and CAD. In 51 patients (49.5 \pm 5.1 years, 64.8% male) who underwent

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64-slice MDCT, we measured threshold-based PCAT volumes using distance and anatomic-based methods. Using the most reproducible method, we performed the proximal 40-mm distance measurement in three groups as stratified by coronary plaque and high-sensitivity C-reactive protein (hs-CRP) levels: Group 1 (presence of coronary plaque, hs-CRP >2.0mg/L); an intermediate group (Group 2, no plaque, hs-CRP >2.0mg/L); and Group 3 (no plaque, hs-CRP <1.0mg/L). We compared PCAT volumes to the presence of coronary plaque on a patient (n=51) and vessel (n=153) basis. On a subsegment basis (n=1224), we compared PCAT volume to the presence of plaque as well as plaque morphology. Distance-based PCAT volume measurements yielded excellent reproducibility with intra-observer intraclass correlation (ICC) of 0.997 and inter-observer ICC of 0.951. On a both a per-patient and per-vessel analysis, adjusted PCAT volume was greater in patients with plaque (Group 1) than without plaque (Groups 2 and 3, p<0.001). No difference in PCAT volume was seen between high and low hs-CRP groups without plaque (p=0.51). Adjusted PCAT volumes were higher in subsegments with plaque as compared without (p<0.001). Additionally, adjusted PCAT volume was greatest in subsegments with mixed plaque followed by non-calcified plaque, calcified plaque, and the lowest volume in segments with no plaque (p<0.001). In this proof-of-concept study, threshold based PCAT volume assessment is feasible and highly reproducible. PCAT volume is increased in patients and vessels with coronary plaques. Surrounding vessel subsegments with coronary plaque, particularly mixed plaques, have greatest PCAT volume and highlight the effect of local PCAT in the development of coronary atherosclerosis.

J Mol Cell Cardiol. 2011 Jul 14. [Epub ahead of print]

PET imaging of cardiac hypoxia: Opportunities and challenges.

Handley MG, Medina RA, Nagel E, Blower PJ, Southworth R.

Myocardial hypoxia is a major factor in the pathology of cardiac ischemia and myocardial infarction. Hypoxia also occurs in microvascular disease and cardiac hypertrophy, and is thought to be a prime determinant of the progression to heart failure, as well as the driving force for compensatory angiogenesis. The non-invasive delineation and quantification of hypoxia in cardiac tissue therefore has the potential to be an invaluable experimental, diagnostic and prognostic biomarker for applications in cardiology. However, at this time there are no validated methodologies sufficiently sensitive or reliable for clinical use. PET imaging provides real-time spatial information on the biodistribution of injected radiolabeled tracer molecules. Its inherent high sensitivity allows quantitative imaging of these tracers, even when injected at sub-pharmacological (\geq pM) concentrations, allowing the non-invasive investigation of biological systems without perturbing them. PET is therefore an attractive approach for the delineation and quantification of cardiac hypoxia and ischemia. In this review we discuss the key concepts which must be considered when imaging hypoxia in the heart. We summarize the PET tracers which are currently available, and we look forward to the next generation of hypoxia-specific PET imaging agents currently being developed. We describe their potential advantages and shortcomings compared to existing imaging approaches, and what is needed in terms of validation and characterization before these agents can be exploited clinically.

Acta Neurol Scand. 2011 Jul 23. doi: 10.1111/j.1600-0404.2011.01576.x. [Epub ahead of print]

Correlation between crossed cerebellar diaschisis and clinical neurological scales.

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Szilágyi G, Vas Á, Kerényi L, Nagy Z, Csiba L, Gulyás B. Correlation between crossed cerebellar diaschisis and clinical neurological scales. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2011.01576.x. © 2011 John Wiley & Sons A/S. Background - A common consequence of unilateral stroke is crossed cerebellar diaschisis (CCD), a decrease in regional blood flow (CBF) and metabolism (CMRglu) in the cerebellar hemisphere contralateral to the affected cerebral hemisphere. Former studies indicated a post-stroke time-dependent relationship between the degree of CCD and the clinical status of acute and sub-acute stroke patients, but no study has been performed in post-stroke patients. Objectives - The objective of this investigation was to evaluate the quantitative correlation between the degree of CCD and the values of clinical stroke scales in post-stroke patients. Materials and Methods - We measured with positron emission tomography (PET) regional CBF and CMRglu values in the affected cortical regions and the contralateral cerebellum in ten ischaemic post-stroke patients. Based on these quantitative parameters, the degree of diaschisis (DoD) was calculated, and the DoD values were correlated with three clinical stroke scales [Barthel Index, Orgogozo Scale and Scandinavian Neurological Scale (SNS)]. Results - There were significant linear correlations between all clinical stroke scales and the CCD values (Barthel Index and Orgogozo Scale: $P < 0.001$, for both CBF and CMRglu; SNS: $P = 0.007$ and $P = 0.044$; CBF and CMRglu, respectively). Conclusions - The findings indicate that DoD can be used as a quantitative indicator of the functional impairments following stroke, i.e. it can serve as a potential surrogate of the severity of the damage.

Arch Cardiol Mex. 2011 Apr-Jun;81(2):154-7.

[The importance of multi-imaging diagnosis in cardiology].

[Article in Spanish]

Alexánderson E, Jácome R, Romero E, Peña-Cabral M, Meléndez G, Kimura-Hayama E, Meave A.

Cardiology

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Cardiovascular imaging is one of the disciplines in cardiology with the most recent advances. This means that the teaching of Cardiology must evolve in the same way. In 2009, the American College of Cardiology published a statement, which points out that all of the cardiology residents must have basic training in every one of the cardiovascular imaging modalities available. Ischemic heart disease is the main cause of death in the world, including Mexico. Up to 43% of the patients that suffered a myocardial infarction and up to 31% of the patients with sudden cardiac death had an almost normal nuclear myocardial perfusion study in the year before the event, thus evidencing the importance of a multi-imaging approach. With the better understanding of the pathophysiological processes of coronary artery disease, new techniques have been developed that allows the detection of this disease almost from the beginning, through the detection of endothelial dysfunction by Positron Emission Tomography. Later on, when the patient develops diffuse atherosclerosis, we can rely on the use of de coronary calcium score and the detection of atherosclerotic plaques with coronary computed tomography angiography. To detect the presence of myocardial ischemia, two methods are widely used: echocardiography and nuclear medicine. Other options to identify myocardial ischemia are magnetic resonance imaging and computed tomography, due to the development of the "Dual Source" and "Flash" technologies. After an acute coronary event, cardiovascular imaging is useful for risk stratification and detection of myocardial viability, being the positron emission tomography the gold standard.

Ann N Y Acad Sci. 2011 Jun;1228:137-49. doi: 10.1111/j.1749-6632.2011.06017.x.

Positron emission tomography for the evaluation and treatment of cardiomyopathy.

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Congestive heart failure accounts for tremendous morbidity and mortality worldwide. There are numerous causes of cardiomyopathy, the most common of which is coronary artery disease. Positron emission tomography (PET) has an established and expanding role in the evaluation of patients with cardiomyopathy. The specific application of PET to hypertrophic cardiomyopathy, cardiac sarcoidosis, and diabetic cardiomyopathy has been studied extensively and promises to be a useful tool for managing these patients. Furthermore, evaluating the efficacy of standard treatments for congestive heart failure is important as health care costs continue to rise. Recently, there have been significant developments in the field of cardiovascular stem cell research. Familiarity with the mechanisms by which stem cells benefit patients with cardiovascular disease is the key to understanding these advances. Molecular imaging techniques including PET/CT imaging play an important role in monitoring stem cell therapy in both animals and humans. These noninvasive imaging techniques will be highlighted in this paper.

Nihon Naika Gakkai Zasshi. 2011 May 10;100(5):1388-90.

[A case of fever of unknown origin that diagnosed as early-phase of Takayasu arteritis by FDG-PET/CT].

[Article in Japanese]

Miyachi H, Kodani E, Okazaki R, Yoshikawa M, Matsumoto S, Endoh Y, Nakagomi A, Kusama Y, Isobe M, Atarashi H.

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J Am Coll Cardiol. 2011 Jun 21;57(25):2507-15.

Imaging of the aortic valve using fluorodeoxyglucose positron emission tomography increased valvular fluorodeoxyglucose uptake in aortic stenosis.

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Because fluorodeoxyglucose positron emission tomography (FDG-PET) imaging provides a noninvasive index of inflammation, we sought to assess whether FDG uptake in the aortic valve (AV) is increased in aortic stenosis (AS). AS is associated with valvular inflammation. FDG-PET/computed tomography data were retrospectively evaluated in 84 patients (age 73 ± 9 years, 45% female), 42 patients with AS, and 42 age-matched controls. FDG uptake was determined within the AV while blinded to AS severity. Target-to-background ratio (TBR) was calculated as valvular/blood activity. Stenosis severity was established on echocardiography, and presence of AV calcification was independently assessed on computed tomography. The aortic valve PET signal (TBR) was increased in AS compared with controls (median 1.53 [interquartile range (IQR): 1.42 to 1.76] vs. 1.34 [IQR: 1.20 to 1.55]; $p < 0.001$). Further, compared with controls, TBR was increased in mild (median 1.50 [IQR: 1.36 to

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1.75]; $p = 0.01$) and moderate (median 1.70 [IQR: 1.52 to 1.94]; $p < 0.001$), but not in severe AS (median 1.49 [IQR: 1.40 to 1.54]; $p = 0.08$). When subjects were categorized according to AV calcification, valvular FDG uptake was increased in mildly (median 1.50 [IQR: 1.36 to 1.79]; $p < 0.01$) and moderately (median 1.67 [IQR: 1.50 to 1.85]; $p < 0.001$), but not severely calcified valves (median 1.51 [IQR: 1.38 to 1.54]; $p = 0.15$), compared with noncalcified valves (median 1.35 [IQR: 1.20 to 1.52]). This study supports the hypothesis that AS is an inflammatory condition and suggests that inflammation may be reduced in late-stage disease. This may have important implications in the design of studies assessing the effect of therapeutic agents in modifying progression of AS.

Cardiology. 2011;118(3):164-7. doi: 10.1159/000328000. Epub 2011 Jun 1.

Positron emission tomography for risk assessment of women investigated for coronary artery disease.

Pianou N, Georgakopoulos A, Anagnostopoulos CD.

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Arch Dermatol. 2011 May 16. [Epub ahead of print]

Systemic and Vascular Inflammation in Patients With Moderate to Severe Psoriasis as Measured by [18F]-Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography (FDG-PET/CT): A Pilot Study.

Mehta NN, Yu Y, Saboury B, Foroughi N, Krishnamoorthy P, Raper A, Baer A, Antigua J, Van Voorhees AS, Torigian DA, Alavi A, Gelfand JM.

Krishnamoorthy, and Antigua, and Mss Yu, Raper, and Baer), Departments of Medicine (Dr Mehta), Radiology (Drs Saboury, Foroughi, Torigian, and Alavi), Dermatology (Drs Voorhees and Gelfand), and Epidemiology and Biostatistics (Dr Gelfand), and Center for Clinical Epidemiology and Biostatistics, School of Medicine (Drs Mehta and Gelfand), University of Pennsylvania, Philadelphia.

To evaluate the feasibility of using [18F]-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET/CT) to detect and quantify systemic inflammation in patients with psoriasis. Case series with a nested case-control study. Referral dermatology and preventive cardiology practices. Six patients with psoriasis affecting more than 10% of their body surface area and 4 controls age and sex matched to 4 of the patients with psoriasis for a nested case-control study. The FDG uptake in the liver, musculoskeletal structures, and aorta measured by mean standardized uptake value, a measure of FDG tracer uptake by macrophages and other inflammatory cells. FDG-PET/CT identified numerous foci of inflammation in 6 patients with psoriasis within the skin, liver, joints, tendons, and aorta. Inflammation in the joints was observed in a patient with psoriatic arthritis as well as in 1 patient with no history of joint disease or joint symptoms. In a nested case-control study, FDG-PET/CT imaging demonstrated increased vascular inflammation in multiple segments of the aorta compared with controls. These findings persisted after adjustment for traditional cardiovascular risk factors in multivariate analysis (mean $\beta = 0.33$; $P < .001$). Patients with psoriasis further demonstrated increased hepatic inflammation after adjusting for cardiovascular risk factors ($\beta = 0.18$; $P < .001$), but the association was no longer significant when adjusted for alcohol intake ($\beta = -0.25$; $P = .07$). Conclusion FDG-PET/CT is a sensitive tool for identifying inflammation and can be used to identify clinically observed inflammation in the skin and subclinical inflammation in the blood vessels, joints, and liver of patients with psoriasis.

J Nucl Cardiol. 2011 Aug;18(4):657-67. Epub 2011 May 13.

Altered myocardial glucose utilization and the reverse mismatch pattern on rubidium-82 perfusion/F-18-FDG PET during the sub-acute phase following reperfusion of acute anterior myocardial infarction.

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Reperfused myocardium post-acute myocardial infarction (AMI) may have altered metabolism with implications for therapy response and function recovery. We explored glucose utilization and the "reverse mismatch" (RMM) pattern (decreased F-18-fluorodeoxyglucose (FDG) uptake relative to perfusion) in patients who underwent mechanical reperfusion with percutaneous coronary intervention (PCI) for AMI. Thirty-one patients with anterior wall AMI treated with acute reperfusion, with left ventricular ejection fraction $\leq 45\%$, underwent rest rubidium-82 (Rb-82) and FDG PET 2-10 days post-AMI. Resting echocardiograms were used to assess wall motion abnormalities. Significant RMM occurred in 15 (48%) patients and was associated with a shorter time to PCI of 2.9 hours (2.2, 13.3 hours) compared to patients without significant RMM: 11.4 hours (3.9, 22.4 hours) ($P = .03$). Within the peri-infarct regions, segments with significant RMM were more likely to have wall motion abnormalities (OR = 2.3 (1.1, 4.7), $P = .02$) compared to segments without significant RMM. RMM is a common pattern on perfusion/FDG PET during the sub-acute phase following reperfusion of AMI and is associated with shorter times to PCI. Within the peri-infarct region, RMM occurs frequently and is more often associated with wall motion abnormalities than segments without RMM. Whether this represents a myocardial metabolic shift during the sub-acute phase of recovery warrants further study.

JACC Cardiovasc Imaging. 2011 May;4(5):557-60.

PET measurement of absolute myocardial blood flow and LV function in dilated cardiomyopathy.

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Crit Pathw Cardiol. 2011 Mar;10(1):41-3. doi: 10.1097/HPC.0b013e31820d6a2e.

The feasibility of Rubidium-82 positron emission tomography stress testing in low-risk chest pain protocol patients.

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To evaluate the feasibility of dipyridamole-induced reversible ischemia on myocardial perfusion positron emission tomography (PET) imaging using Rubidium-82 (Rb-82 PET) to predict the presence of acute coronary syndrome (ACS) in emergency department (ED) chest pain patients at low risk who were admitted to an observation unit. Retrospective cross-sectional study of electronic medical records after computerized record retrieval. We matched all ED chest pain visits to a database of all scans read by cardiology between January 1, 2004 and January 1, 2006. A PET scan was performed at the ED physician's discretion after a negative observation unit workup, including serial cardiac biomarkers and ECGs. Data were collected on a standardized abstraction instrument. There were 7,691 ED visits for chest pain. Among these patients, 1177 had an Rb-82 PET. Fifty four (4.6%) of these patients had an abnormal or probably abnormal scan. Of these, 28 had catheter-proven significant coronary disease, requiring either revascularization or intensive medical management; 22 patients had ACS by clinical assessment but did not undergo catheterization. Four had no coronary artery disease on catheterization. In a low-risk chest pain population, cardiac PET imaging had true-positive cardiac catheterization rates which were comparable to prior studies of SPECT sestimibi imaging and coronary CTA imaging. With the rapid dissemination of PET technology, and superior performance compared to current imaging methods, myocardial perfusion PET is a feasible alternative to traditional provocative testing in an ED observation unit.

J Nucl Cardiol. 2011 Aug;18(4):744-7.

Cardiac tamponade on ECG-gated dipyridamole PET perfusion imaging.

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J Nucl Cardiol. 2011 Aug;18(4):717-28.

PET imaging of aortic atherosclerosis: Is combined imaging of plaque anatomy and function an amaranthine quest or conceivable reality?

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Traditionally, blood vessels have been studied using contrast luminography to determine the site, extent and severity of luminal compromise by atherosclerotic deposits. Similar anatomical data can now be acquired non-invasively using ultrasound, computed tomography or magnetic resonance imaging. Plaque stability is an important determinant of subsequent vascular events and currently functional data on the stability of plaque is less well provided by these methods. The search for non-invasive techniques to image combined plaque anatomy and function has been pursued with visionary anticipation. This expectation may soon be realised as imaging with radionuclide-labelled atheroma-targeted contrast agents has demonstrated that plaque functional characteristics can now be shown. Increasingly positron emission tomography/computed tomography (PET/CT) imaging with (18)F fluorodeoxyglucose (FDG) and other radionuclides is being used to determine culprit plaques in complex clinically scenarios. Clinically, this information may prove extremely valuable in the assessment of stable and unstable patients and its use in prime time medical practice is eagerly awaited. We will discuss the current clinical applications of functional atheroma imaging in the aorta and highlight the promising preclinical data on novel image biomarkers of plaque instability. If clinical science is able to successfully translate these advances in vascular imaging from the bench to the bedside, a new paradigm will be achieved in cardiovascular diagnostics.

J Cardiovasc Transl Res. 2011 Aug;4(4):514-22. Epub 2011 May 3.

Imaging cardiac stem cell therapy: translations to human clinical studies.

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Stem cell therapy promises to open exciting new options in the treatment of cardiovascular diseases. Although feasible and clinically safe, the in vivo behavior and integration of stem cell transplants still remain largely unknown. Thus, the development of innovative non-invasive imaging techniques capable of effectively tracking such therapy in vivo is vital for a more in-depth investigation into future clinical applications. Such imaging modalities will not only generate further insight into the mechanisms behind stem cell-based therapy, but also address some major concerns associated with translational cardiovascular stem cell therapy. In the present review, we summarize the principles underlying three major stem cell tracking methods: (1) radioactive labeling for positron emission tomography (PET) and single photon emission computed tomography (SPECT) imaging, (2) iron particle labeling for magnetic resonance imaging (MRI), and (3) reporter gene labeling for bioluminescence, fluorescence, MRI, SPECT, and PET imaging. We then discuss recent clinical studies that have utilized these modalities to gain biological insights into stem cell fate.

Chin Med J (Engl). 2011 Mar;124(6):911-7.

Imaging of atherosclerotic aorta of rabbit model by detection of plaque inflammation with fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography.

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Atherosclerotic plaque rupture is the primary mechanism of thrombosis which plays a key role in the onset of acute coronary syndromes. Detection of these plaques prone to rupture (vulnerable plaque) could be clinically significant for prevention of cardiac events. It has been shown that high metabolism cells have a high uptake of fluorine-18 fluorodeoxyglucose ((¹⁸F)-FDG). The objective of this study was to investigate the correlation of FDG uptake and the immuno-histochemistry parameters of plaques, and the effect of atorvastatin on vulnerable atherosclerotic plaque in a rabbit model. Ten male New Zealand White rabbits were divided into three groups as follows: (1) normal control group (n = 2, C group): the animals were fed a standard diet at 120 g/d and were given water ad libitum; (2) atherosclerosis group (n = 4, As group): animals were fed with high fat diet for 5 months after aortic endothelia damage; (3) treatment group (atherosclerosis + atorvastatin, n = 4, Statin group): animals were fed with high fat diet for 5 months and then changed into normal chow plus atorvastatin (2.5 mg·d⁻¹·kg⁻¹) treatment for another 4 months. Then these four rabbits were imaged with fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (PET/CT) and sacrificed for pathohistologic studies. FDG uptake by the aorta was expressed as target-to-background ratio (TBR). Maximal standardized uptake value (SUV) was measured over the thoracic and abdominal aortas. The aortic smooth muscle cell (SMC) number, CD-14 antibody positive cell (macrophage) number and the ratio of the thickness of fibrous cap to the thickness of lipid core (cap-to-core ratio) in atherosclerotic plaques were analyzed. As group showed significantly higher uptake of FDG than C group (SUVs: 0.746 ± 0.172 vs. 0.286 ± 0.073, P < 0.001). After 4 months of atorvastatin treatment and the modification of diet, SUVs decreased significantly (Statin group: 0.550 ± 0.134, compared to As group, P < 0.001). However, no marked difference was found in TBR, the number of macrophages, the number of SMC and the cap-to-core ratio in the aortic segments between Statin group and As group. The correlation of aortic FDG uptake with SMC assessed by histopathology was negatively significant (r = -0.57, P < 0.001). When aortic FDG uptake was expressed as TBR, it correlated significantly (r = 0.69, P < 0.001) with the macrophage number, and also correlated significantly (r = -0.78, P < 0.001) with the cap-to-core ratio. (¹⁸F)-FDG PET/CT might serve as a useful non-invasive imaging technique for detection of atherosclerotic plaque and potentially permit monitoring of relative changes in inflammation within the atherosclerotic lesion.

Am J Physiol Heart Circ Physiol. 2011 Jul;301(1):H129-37. Epub 2011 Apr 13.

Effects of alcohol septal ablation on coronary microvascular function and myocardial energetics in hypertrophic obstructive cardiomyopathy.

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This study investigated the effects of alcohol septal ablation (ASA) on microcirculatory function and myocardial energetics in patients with hypertrophic cardiomyopathy (HCM) and left ventricular outflow tract (LVOT) obstruction. In 15 HCM patients who underwent ASA, echocardiography was performed before and 6 mo after the procedure to assess the LVOT gradient (LVOTG). Additionally, [(15)O]water PET was performed to obtain resting myocardial blood flow (MBF) and coronary vasodilator reserve (CVR). Changes in LV mass (LVM) and

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volumes were assessed by cardiovascular magnetic resonance imaging. Myocardial oxygen consumption (MVo(2)) was evaluated by [(11)C]acetate PET in a subset of seven patients to calculate myocardial external efficiency (MEE). After ASA, peak LVOTG decreased from 41 ± 32 to 23 ± 19 mmHg ($P = 0.04$), as well as LVM (215 ± 74 to 169 ± 63 g; $P < 0.001$). MBF remained unchanged (0.94 ± 0.23 to 0.98 ± 0.15 ml·min⁻¹·g⁻¹; $P = 0.45$), whereas CVR increased (2.55 ± 1.23 to 3.05 ± 1.24 ; $P = 0.05$). Preoperatively, the endo-to-epicardial MBF ratio was lower during hyperemia compared with rest (0.80 ± 0.18 vs. 1.18 ± 0.15 ; $P < 0.001$). After ASA, the endo-to-epicardial hyperemic (h)MBF ratio increased to 1.03 ± 0.26 ($P = 0.02$). Δ CVR was correlated to Δ LVOTG ($r = -0.82$; $P < 0.001$) and Δ LVM ($r = -0.54$; $P = 0.04$). MEE increased from 15 ± 6 to $20 \pm 9\%$ ($P = 0.04$). Coronary microvascular dysfunction in obstructive HCM is at least in part reversible by relief of LVOT obstruction. After ASA, hMBF and CVR increased predominantly in the subendocardium. The improvement in CVR was closely correlated to the absolute reduction in peak LVOTG, suggesting a pronounced effect of LV loading conditions on microvascular function of the subendocardium. Furthermore, ASA has favorable effects on myocardial energetics.

JACC Cardiovasc Imaging. 2011 Mar;4(3):292-302.

Cardiac PET: a versatile, quantitative measurement tool for heart failure management.

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Current American Heart Association/American College of Cardiology practice guidelines classify congestive heart failure (CHF) in 4 stages (A, B, C, and D). This review focuses on state-of-the-art and future applications of quantitative positron emission tomography (PET) myocardial perfusion and metabolic imaging in the clinical evaluation and treatment of patients in all CHF stages. Basic physiological and metabolic principles related to the regulation of myocardial blood flow and metabolism at various stages of CHF are briefly reviewed. The advantages of quantitative PET image analysis in contrast to simple qualitative visual analysis of the scans also will be addressed. Finally, potential future clinical applications of quantitative PET for CHF evaluation and treatment will be discussed.

Phys Med Biol. 2011 Apr 7;56(7):2145-60. Epub 2011 Mar 9.

Preliminary study of the detectability of coronary plaque with PET.

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The evaluation of coronary plaque vulnerability could be of great diagnostic value in cardiology. Positron emission tomography (PET) is a good candidate due to its ability to quantify micromolar concentrations of targeted drugs. However, the detectability of sub-voxel targets such as coronary plaque is limited by partial volume effects and by cardiorespiratory motion. The goal of this paper is to investigate the impact of these factors in the detectability of plaque uptake. Radioactive markers were implanted on the epicardium of a pig and in vivo scans were performed. This was complemented with phantom measurements to determine the minimum detectable uptake as a function of background activity. Simulations were used to evaluate the effect of cardiorespiratory motion on the reconstructed lesions. Despite cardiorespiratory motion of up to 7 mm, the markers were detectable in the in vivo scans even after the injection of background. A lower limit of 250 Bq was found for a target to be detectable. Motion reduced the contrast of the reconstructed lesions to 23% of their static counterpart. Respiratory gating improved this to 49% of the static value. The results suggest that coronary plaque evaluation with PET is possible, provided that sufficient plaque-to-myocardium uptake contrast (50 to 100) can be achieved. This requirement increases exponentially for lesions with uptake below 250 Bq. The described experiments provide a means of estimating the minimum uptake and contrast required to ensure the detectability of plaque lesions.

Cardiology. 2010;117(4):301-6. Epub 2011 Mar 2.

Prognosis of a normal positron emission tomography ⁸²Rb myocardial perfusion imaging study in women with no history of coronary disease.

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Myocardial perfusion imaging (MPI) with positron emission tomography (PET) has advantages over single-photon emission computerized tomography, particularly for women. This investigation was undertaken to define the prognosis of a normal stress PET MPI study in women. The cohort comprised 457 women evaluated for suspected coronary artery disease (CAD) who had normal pharmacologic stress (⁸²Rb PET MPI). No patient had clinically evident CAD. Kaplan-Meier estimates were used to determine death and initial nonfatal cardiac event rates over 7 years. Log rank tests were used to assess the relationship between baseline cardiac risk and events during follow-up, and to contrast survival in the

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cohort with age- and gender-matched US census comparators. During follow-up, there were 11 deaths (all nonischemic), 3 nonfatal myocardial infarctions, 3 percutaneous coronary interventions and 1 coronary artery bypass operation. Average risks of death and initial nonfatal cardiac events were 0.72 and 0.47% per year, respectively. Cardiac events were associated with a history of diabetes ($p < 0.0003$) and a family history of CAD ($p < 0.05$). A normal cardiac PET study is associated with a very low rate of future cardiac events. Women with diabetes and a strong family history of CAD are more likely to sustain events and require close surveillance for the development of coronary disease.

Ugeskr Laeger. 2011 Feb 21;173(8):567-72.

[82 Rubidium PET to replace myocardial scintigraphy].

[Article in Danish]

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Since the 1970's nuclear cardiology has mainly been based on the use of gamma camera technology. While gamma cameras have undergone a rapid development, the number of perfusion tracers has been limited. In parallel, cardiac positron emission tomography (PET) has only been performed with short-lived isotopes at centres with access to a cyclotron, and only including a very limited number of patients. The number of PET scanners has increased markedly in Denmark and with the introduction of generator-produced 82-Rubidium, this modality may replace the traditional cardiac single photon emission computed tomography (SPECT).

J Am Coll Cardiol. 2011 Feb 22;57(8):971-6.

Positron emission tomography measurement of periodontal (18)f-fluorodeoxyglucose uptake is associated with histologically determined carotid plaque inflammation.

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This study aimed to test the hypothesis that metabolic activity within periodontal tissue (a possible surrogate for periodontal inflammation) predicts inflammation in a remote atherosclerotic vessel, utilizing (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) imaging. Several lines of evidence establish periodontal disease as an important risk factor for atherosclerosis. FDG-PET imaging is an established method for measuring metabolic activity in human tissues and blood vessels. One hundred twelve patients underwent FDG-PET imaging 92 ± 5 min after FDG administration (13 to 25 mCi). Periodontal FDG uptake was measured by obtaining standardized uptake values from the periodontal tissue of each patient, and the ratio of periodontal to background (blood) activity was determined (TBR). Standardized uptake value measurements were obtained in the carotid and aorta as well as in a venous structure. Localization of periodontal, carotid, and aortic activity was facilitated by PET coregistration with computed tomography or magnetic resonance imaging. A subset of 16 patients underwent carotid endarterectomy within 1 month of PET imaging, during which atherosclerotic plaques were removed and subsequently stained with anti-CD68 antibodies to quantify macrophage infiltration. Periodontal FDG uptake was compared with carotid plaque macrophage infiltration. Periodontal FDG uptake (TBR) is associated with carotid TBR ($R = 0.64$, $p < 0.0001$), as well as aortic TBR ($R = 0.38$; $p = 0.029$). Moreover, a strong relationship was observed between periodontal TBR and histologically assessed inflammation within excised carotid artery plaques ($R = 0.81$, $p < 0.001$). FDG-PET measurements of metabolic activity within periodontal tissue correlate with macrophage infiltration within carotid plaques. These findings provide direct evidence for an association between periodontal disease and atherosclerotic inflammation.

J Nucl Cardiol. 2011 Apr;18(2):371-4.

Fasting FDG PET compared to MPI SPECT in cardiac sarcoidosis.

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Uptake of F-18 FDG and ultrasound analysis of carotid plaque.

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To elucidate the relation between the echolucent plaque on carotid ultrasound and acute inflammation on F-18 FDG carotid PET/CT. Thirty nine patients (M:F ratio = 23:16, mean age = 63 ± 11 years) that underwent coronary angiography and carotid ultrasound were divided into three groups-echolucent plaque (n = 22), calcified (n = 10), and no plaque (n = 7). All the patients underwent F-18 FDG carotid PET/CT. The mean standardized uptake values (SUV), namely target to background ratio (TBR) on 180 minutes delayed F-18 FDG carotid PET/CT images were compared with levels of serum inflammatory markers and lipid profiles, and in terms of the presence of carotid plaque on carotid US. 180 minutes TBR of carotid arterial wall at echolucent plaque, calcified plaque, and no plaque were 1.40 ± 0.05 , 1.23 ± 0.03 , 1.17 ± 0.03 in both carotid artery. TBR of carotid arterial walls for echolucent plaque were significantly larger than TBR for calcified, and no plaque respectively at the both side of carotid artery ($P < .05$). Serum HDL levels were found to be inversely correlated with F-18 FDG uptake at both carotid arteries ($r = -0.43$, $P = .005$) on 180 minutes delayed phase images. Also serum hs-CRP levels were found to be correlated with F-18 FDG TBR values of right carotid arteries ($r = 0.41$, $P = .04$). Our results show that F-18 FDG carotid PET/CT can depict metabolically active atherosclerotic plaques, and suggest that F-18 FDG carotid PET/CT can be used as a noninvasive imaging modality for functional evaluation of atherosclerosis.

J Nucl Med. 2011 Feb;52(2):263-9.

PET of (R)-11C-rolipram binding to phosphodiesterase-4 is reproducible and sensitive to increased norepinephrine in the rat heart.

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Phosphodiesterase-4 (PDE4) plays a critical role in the regulation of β -adrenergic receptor-stimulated cyclic adenosine monophosphate cell signaling in the heart. (R)-rolipram, a PDE4-selective inhibitor, has been studied previously as a radiotracer for the quantification of PDE4 levels. The aim of this study was to characterize (R)-(11)C-rolipram binding in the rat myocardium in vivo, using small-animal PET. Male Sprague-Dawley rats (n = 30) were administered (R)-(11)C-rolipram and imaged for 60 min to evaluate tracer binding and reproducibility, quantified using Logan slope analysis of the distribution volume. Dynamic (13)N-ammonia imaging was performed to quantify myocardial blood flow and assist in cardiac regional analysis. Saturation studies evaluated the sensitivity of (R)-(11)C-rolipram to PDE4 blocking by unlabeled cold (R)-rolipram (0.0001-1.0 mg/kg), for estimation of the median effective dose (ED(50)) in the heart. (R)-(11)C-rolipram response to enhanced norepinephrine stimulation of the β -adrenergic receptor with desipramine (20 mg/kg, intravenous) was also studied. Intrarat variability studies (n = 5) were conducted with test-retest imaging at 16 ± 7 d. A reduction of Logan slope was observed with increasing cold mass coadministered with the tracer, with an ED(50) of 0.0019 mg/kg (95% confidence interval, 0.0014-0.0052) estimated from the saturation studies. This ED(50) predicted less than 10% enzyme occupancy at 0.0002 mg of cold (R)-rolipram per kilogram (mass/body weight). Low-occupancy imaging at 0.00018 ± 0.00002 mg/kg produced a mean Logan slope of 5.5 ± 0.85 mL/cm(3). Enzyme saturation of more than 90%, compared with low-occupancy conditions, occurred at more than 0.02 mg/kg, with a complete blocking dose (>1 mg of (R)-rolipram per kilogram) resulting in a Logan slope of 3.3 ± 0.1 mL/cm(3), representing a 40% reduction. Compared with baseline, a Logan slope of 6.8 ± 0.7 mL/cm(3) in desipramine-challenged animals was observed, representing a 30% increase due to acute norepinephrine stimulation, despite a reduction in myocardial blood flow. Intrarat and intraoperator variability was less than 5% between repeated measures. (R)-(11)C-rolipram shows the ability to monitor increases and decreases in PDE4 availability in the rat myocardium, with good reproducibility.

Cardiovasc Res. 2011 Jun 1;90(3):546-56. Epub 2011 Jan 21.

Placental stem cells pre-treated with a hyaluronan mixed ester of butyric and retinoic acid to cure infarcted pig hearts: a multimodal study.

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Pre-treating placenta-derived human mesenchymal stem cells (FMhMSCs) with a hyaluronan mixed ester of butyric and retinoic acid (HBR) potentiates their reparative capacity in rodent hearts. Our aim was to test FMhMSCs in a large-animal model by employing a novel combination of in vivo and ex vivo analyses. Matched regional quantifications of myocardial function and viability were performed by magnetic resonance imaging (MRI) and positron emission tomography (PET) 4 weeks after myocardial infarction combined with intramyocardial injection of FMhMSCs (n = 7), or HBR-pre-treated FMhMSCs (HBR-FMhMSCs, n = 6), or saline solution (PBS, n = 7). Sham-operated pigs (n = 4) were used as control animals. Despite no differences in the ejection fraction and haemodynamics, regional MRI revealed, in pigs treated with HBR-FMhMSCs compared with the other infarcted groups, a 40% smaller infarct scar size and a significant improvement of the end-systolic wall

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thickening and circumferential shortening of the infarct border zone. Consistently, PET showed that myocardial perfusion and glucose uptake were, respectively, 35 and 23% higher in the border zone of pigs treated with HBR-FMhMSCs compared with the other infarcted groups. Histology supported *in vivo* imaging; the delivery of HBR-FMhMSCs significantly enhanced capillary density and decreased fibrous tissue by approximately 68%. Moreover, proteomic analysis of the border zone in the HBR-FMhMSCs group and the FMhMSCs group indicated, respectively, 45 and 30% phenotypic homology with healthy tissue, while this homology was only 26% in the border zone of the PBS group. Our results support a more pronounced reparative potential of HBR-pre-treated FMhMSCs in a clinically relevant animal model of infarction and highlight the necessity of using combined diagnostic imaging to avoid underestimations of stem cell therapeutic effects in the heart.

Curr Cardiol Rep. 2011 Apr;13(2):121-31.

Fatty acid imaging of the heart.

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Imaging metabolic processes in the human heart yields valuable insights into the mechanisms contributing to myocardial pathology and allows assessment of the efficacy of therapies designed to treat cardiac disease. Recent advances in fatty acid (FA) imaging using positron emission tomography (PET) include the development of a method to assess endogenous triglyceride metabolism and the design of new fluorine-18 labeled tracers. Studies of patients with diabetes have shown that the heart is resistant to insulin-mediated glucose uptake and that metabolism of nonesterified FA is upregulated. Cardiac PET imaging has also recently shown the increase in myocardial FA uptake seen in obese patients can be reversed with weight loss. And a pilot study of patients with chronic kidney disease demonstrated that PET imaging can reveal myocardial metabolic alterations that parallel the decline in estimated glomerular filtration rate. Recent advances in FA imaging using single photon emission computed tomography (SPECT) have been accomplished with the tracer β -methyl-p-[(123)I]-iodophenyl-pentadecanoic acid (BMIPP). Two meta-analyses showed this imaging technique has a diagnostic accuracy for the detection of obstructive coronary artery disease that compares favorably with SPECT myocardial perfusion imaging and that BMIPP imaging yields excellent prognostic data in patients across the spectrum of coronary artery disease. A recent multicenter study of patients presenting with acute coronary syndromes found BMIPP SPECT imaging has greater diagnostic sensitivity than, and enhances the negative predictive value of, clinical assessment alone. Because of their exquisite sensitivity, nuclear imaging techniques facilitate the study of physiologic processes that are the key to our understanding of cardiac metabolism in health and disease.

Curr Cardiol Rep. 2011 Apr;13(2):151-8.

Microvascular angina: assessment of coronary blood flow, flow reserve, and metabolism.

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Microvascular angina (MVA) is an often overlooked cause of significant chest pain. Decreased myocardial perfusion secondary to dysregulated blood flow in the microvasculature can occur in the presence or absence of obstructive epicardial coronary artery disease. The corresponding myocardial ischemia and angina is now a well-established diagnosis, made by detection of decreased coronary flow reserve (CFR). Although low CFR and MVA are associated with poor prognosis, there is initial evidence for reversibility of this abnormal vascular regulation with aggressive medical therapy and control of associated risk factors. Current assessment of MVA is carried out predominantly during cardiac catheterization; however, noninvasive techniques to assess CFR are being developed, including PET, MRI, and CT modalities. Quantitative tracer techniques or imaging of metabolic disturbances reflecting ischemia will likely enhance diagnostic approaches for such patients as well as allow more frequent monitoring of response to therapy.

J Nucl Med. 2011 Feb;52(2):303-10. Epub 2011 Jan 13.

Variations in clinical PET/CT operations: results of an international survey of active PET/CT users.

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This study gathered information about clinical PET/CT operations worldwide to help guide discussions on the use and standardization of clinical PET/CT. A Web-based survey of PET/CT users was initiated in November 2009 through e-mail advertising using Academy of Molecular Imaging databases. Recipients were asked 58 questions related to demographics (e.g., location, number of PET/CT systems, and staffing), PET/CT operations and use, and variations in (18)F-FDG oncology imaging protocols. The responders were from centers in the Americas (71%), Europe (22%), Asia-Pacific (6%), and Middle East (1%), with most responding sites representing public health care institutions (60%). PET/CT

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systems were most frequently installed in nuclear medicine departments (59%). Of the sites operating a PET/CT system, 16% had 10 y or more of stand-alone PET experience. About 40% of all sites operated at least 2 PET/CT systems. PET/CT was most frequently used for applications in torso or whole-body oncology (87%), radiation therapy planning (4%), cardiology (4%), and neurology (5%). The average interval of fasting before an (18)F-FDG PET/CT examination was 7 ± 3 h (range, 4-12 h). Blood glucose levels were measured at 99% of sites, but acceptable maximal glucose levels varied substantially (an upper limit of 200 mg/dL was applied at >50% of the institutions). A weight-based radioactivity dose injection was performed at 44% of sites. The mean (18)F-FDG activity injected was 390 MBq (range, 110-585 MBq) for 3-dimensional PET of a 75-kg patient. The mean uptake time was 64 ± 14 min (range, 20-90 min). Split protocols involving patient repositioning and adapted imaging parameters were used at 51% of sites. Only 41% used patient positioning aids. Intravenous or oral CT contrast material was used at 52% of sites in up to 25% of patients. Most sites (90%) measured maximum standardized uptake value as an index of tissue glucose use. Only 62% of sites provided a fully integrated PET/CT report. An international survey among clinical PET/CT users revealed significant variations in standard (18)F-FDG PET/CT protocols. This finding illustrates the need for continuous training and ongoing standardization in an effort to optimize PET/CT in oncology.

J Nucl Cardiol. 2011 Apr;18(2):247-58. Epub 2010 Dec 24.

Partial volume correction incorporating Rb-82 positron range for quantitative myocardial perfusion PET based on systolic-diastolic activity ratios and phantom measurements.

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Quantitative myocardial PET perfusion imaging requires partial volume corrections. Patients underwent ECG-gated, rest-dipyridamole, myocardial perfusion PET using Rb-82 decay corrected in Bq/cc for diastolic, systolic, and combined whole cycle ungated images. Diastolic partial volume correction relative to systole was determined from the systolic/diastolic activity ratio, systolic partial volume correction from phantom dimensions comparable to systolic LV wall thicknesses and whole heart cycle partial volume correction for ungated images from fractional systolic-diastolic duration for systolic and diastolic partial volume corrections. For 264 PET perfusion images from 159 patients (105 rest-stress image pairs, 54 individual rest or stress images), average resting diastolic partial volume correction relative to systole was 1.14 ± 0.04 , independent of heart rate and within $\pm 1.8\%$ of stress images (1.16 ± 0.04). Diastolic partial volume corrections combined with those for phantom dimensions comparable to systolic LV wall thickness gave an average whole heart cycle partial volume correction for ungated images of 1.23 for Rb-82 compared to 1.14 if positron range were negligible as for F-18. Quantitative myocardial PET perfusion imaging requires partial volume correction, herein demonstrated clinically from systolic/diastolic absolute activity ratios combined with phantom data accounting for Rb-82 positron range.

Nuklearmedizin. 2011;50(1):9-14. Epub 2010 Dec 17.

Assessment of left ventricular volumes, ejection fraction and mass. Comparison of model-based analysis of ECG-gated (123m)Tc-SPECT and 18F-FDG-PET.

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We compared and delineated possible differences of model-based analysis of ECG-gated SPECT using (123m)Tc-sestamibi (Tc-SPECT) with ECG-gated 18F-fluorodeoxyglucose-PET (FDG-PET) for determination of end-diastolic (EDV) and end-systolic (ESV) cardiac volumes, left ventricular ejection fraction (LVEF), and myocardial mass (LVMM). 24 patients (21 men; age: 54 ± 12 years) with coronary artery disease underwent Tc-SPECT and FDG-PET imaging for evaluation of myocardial perfusion and viability. By using model-based analysis EDV, ESV, LVEF and LVMM were calculated from short axis images of both Tc-SPECT and FDG-PET. Left ventricular volumes by Tc-SPECT and FDG-PET were 176 ± 60 ml and 181 ± 59 ml for EDV, and 97 ± 44 ml and 103 ± 45 ml for ESV respectively, LVEF was $47 \pm 8\%$ by Tc-SPECT and $45 \pm 9\%$ by FDG-PET. The LVMM was 214 ± 40 g (Tc-SPECT) and 202 ± 43 g (FDG-PET) (all $p = \text{NS}$, paired t-test). A significant correlation was observed between Tc-SPECT and FDG-PET imaging for calculation of EDV ($r = 0.93$), ESV ($r = 0.93$), LVEF ($r = 0.83$) and LVMM ($r = 0.72$). ECG-gated Tc-SPECT and FDG-PET using two tracers with different characteristics (perfusion versus metabolism) showed close agreement concerning measurements of left ventricular volumes, contractile function and myocardial mass by using a model-based analysis.

J Nucl Cardiol. 2011 Feb;18(1):135-43.

Novel iodinated tracers, MIBG and BMIPP, for nuclear cardiology.

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Cardiology

With the rapid growth of molecular biology, in vivo imaging of such molecular process (i.e., molecular imaging) has been well developed. The molecular imaging has been focused on justifying advanced treatments and for assessing the treatment effects. Most of molecular imaging has been developed using PET camera and suitable PET radiopharmaceuticals. However, this technique cannot be widely available and we need alternative approach. ^{123}I -labeled compounds have been also suitable for molecular imaging using single-photon computed tomography (SPECT) ^{123}I -labeled meta-iodobenzylguanidine (MIBG) has been used for assessing severity of heart failure and prognosis. In addition, it has a potential role to predict fatal arrhythmia, particularly for those who had and are planned to receive implantable cardioverter-defibrillator treatment. ^{123}I -beta-methyl-iodophenylpentadecanoic acid (BMIPP) plays an important role for identifying ischemia at rest, based on the unique capability to represent persistent metabolic alteration after recovery of ischemia, so called ischemic memory. Since BMIPP abnormalities may represent severe ischemia or jeopardized myocardium, it may permit risk analysis in CAD patients, particularly for those with chronic kidney disease and/or hemodialysis patients. This review will discuss about recent development of these important iodinated compounds.

Nucl Med Commun. 2011 Jan;32(1):59-62.

Reappraisal of a single-tissue compartment model for estimation of myocardial oxygen consumption by [11C]acetate PET: an alternative to conventional monoexponential curve fitting.

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Myocardial washout kinetics of carbon-11 labelled acetate ([11C]acetate) by positron emission tomography (PET) closely correlate with myocardial oxygen consumption (MVO₂). Analysis of the tissue time activity curve by conventional monoexponential curve fitting, however, does not account for spillover effects and recirculating 11C activity. In theory, a compartment model considering variations of the arterial input function and metabolic 11C contamination, could improve consistency of MVO₂ estimations. The objective of the study was to investigate this hypothesis. Nineteen healthy volunteers were studied under resting conditions with [11C]acetate PET. Time activity curves were analysed by automated monoexponential curve fitting and a single-tissue compartment model to obtain K_{mono} and k₂, as noninvasive indices of MVO₂. Subsequently, K_{mono} and k₂ were related to the rate-pressure product, as an indirect marker of MVO₂. The rate-pressure product was significantly correlated to K_{mono} (r=0.46, P=0.047) and k₂ (r=0.75, P<0.001). The results of this study suggest that a single-tissue compartment model yields more accurate noninvasive estimates of MVO₂ by the use of [11C]acetate PET in humans, in comparison with monoexponential curve fitting.

Heart Fail Rev. 2011 Jul;16(4):411-23.

The role of nuclear imaging in the failing heart: myocardial blood flow, sympathetic innervation, and future applications.

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Heart failure represents a common disease affecting approximately 5 million patients in the United States. Several conditions play an important role in the development and progression of heart failure, including abnormalities in myocardial blood flow and sympathetic innervation. Nuclear imaging represents the only imaging modality with sufficient sensitivity to assess myocardial blood flow and sympathetic innervation of the failing heart. Although nuclear imaging with single-photon emission computed tomography (SPECT) is most commonly used for the evaluation of myocardial perfusion, positron emission tomography (PET) allows absolute quantification of myocardial blood flow beyond the assessment of relative myocardial perfusion. Both techniques can be used for evaluation of diagnosis, treatment options, and prognosis in heart failure patients. Besides myocardial blood flow, cardiac sympathetic innervation represents another important parameter in patients with heart failure. Currently, sympathetic nerve imaging with 123-iodine metaiodobenzylguanidine (123-I MIBG) is often used for the assessment of cardiac innervation. A large number of studies have shown that an abnormal myocardial sympathetic innervation, as assessed with 123-I MIBG imaging, is associated with increased mortality and morbidity rates in patients with heart failure. Also, cardiac 123-I MIBG imaging can be used to risk stratify patients for ventricular arrhythmias or sudden cardiac death. Furthermore, novel nuclear imaging techniques are being developed that may provide more detailed information for the detection of heart failure in an early phase as well as for monitoring the effects of new therapeutic interventions in patients with heart failure.

Eur J Nucl Med Mol Imaging. 2011 Jan;38(1):201-12.

Hybrid cardiac imaging: SPECT/CT and PET/CT. A joint position statement by the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC).

Flotats A, Knuuti J, Gutberlet M, Marcassa C, Bengel FM, Kaufmann PA, Rees MR, Hesse B; Cardiovascular Committee of the EANM, the ESCR and the ECNC.

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Cardiology

Improvements in software and hardware have enabled the integration of dual imaging modalities into hybrid systems, which allow combined acquisition of the different data sets. Integration of positron emission tomography (PET) and computed tomography (CT) scanners into PET/CT systems has shown improvement in the management of patients with cancer over stand-alone acquired CT and PET images. Hybrid cardiac imaging either with single photon emission computed tomography (SPECT) or PET combined with CT depicts cardiac and vascular anatomical abnormalities and their physiologic consequences in a single setting and appears to offer superior information compared with either stand-alone or side-by-side interpretation of the data sets in patients with known or suspected coronary artery disease (CAD). Hybrid systems are also advantageous for the patient because of the single short dual data acquisition. However, hybrid cardiac imaging has also generated controversy with regard to which patients should undergo such integrated examination for clinical effectiveness and minimization of costs and radiation dose, and if software-based fusion of images obtained separately would be a useful alternative. The European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR) and the European Council of Nuclear Cardiology (ECNC) in this paper want to present a position statement of the institutions on the current roles of SPECT/CT and PET/CT hybrid cardiac imaging in patients with known or suspected CAD.

Neurology

Clin Nucl Med. 2011 Oct;36(10):910-1.

Ga-68-DOTA-NOC PET/CT Reveals Active Graves' Orbitopathy in a Single Extraorbital Muscle.

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A 53-year-old woman with clinical history of multiple stroke presented with bilateral chemosis and vertical paresis of the right eye. Ophthalmologic examination showed partial atrophy of the right optical nerve, without exophthalmos. Sonography presented a pattern suggestive of autoimmune thyropathy. Laboratory revealed subclinical hyperthyroidism, and mildly elevated thyrotropin receptor antibody to 1.3 U/l. Graves' thyroid disease and concomitant ophthalmopathy was assumed. Head and neck Ga-68-DOTA-NOC PET/CT demonstrated marked accumulation at the thyroid and the right rectus inferior muscle. This finding corresponded to an isolated muscular enlargement seen with CT and MRI and representing active endocrine orbitopathy at this single location.

J Affect Disord. 2011 Sep 2. [Epub ahead of print]

Mapping the depressed brain: A meta-analysis of structural and functional alterations in major depressive disorder.

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Depression has a lifetime prevalence of up to 20%. Neuroimaging methods have revealed various structural and functional changes that occur in a human brain during a depressive episode. However, we still lack information concerning the extent to which structural and functional changes co-occur in a depressed brain. Furthermore, it is difficult to evaluate from a merely qualitative literature review what regional brain changes in volume and activation are robust across depressed patient samples and consistent across imaging centers. This study is a meta-analysis from 10 selected studies published previously. We applied the statistical anatomical/activation likelihood estimate method (ALE) in a total of 176 depressed patients and 175 controls for the MRI modality and in a total of 102 depressed patients and 94 controls for the PET modality to quantitatively identify those brain regions that show concordant alteration in the midst of a depressive episode across imaging modalities and study sites. We find a convergent change in the limbic-cortical brain circuit in depression compared to controls of both Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) data. The specific changes include lower gray matter volumes in the amygdala, the dorsal frontomedian cortex, and the right paracingulate cortex, as well as increases in glucose metabolism in the right subgenual and pregenual anterior cingulate cortices. Our current findings represent an important first step towards a more focused approach to neuroimaging unipolar depression. The regions identified could serve as a specific region-of-interest-for-disease template for both individual in vivo imaging studies and postmortem histopathologic exploration.

J Am Geriatr Soc. 2011 Aug 24. doi: 10.1111/j.1532-5415.2011.03539.x. [Epub ahead of print]

Value of Neuropsychological Tests, Neuroimaging, and Biomarkers for Diagnosing Alzheimer's Disease in Younger and Older Age Cohorts.

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To examine the influence of age on the value of four techniques for diagnosing Alzheimer's disease (AD). Observational cohort study. mAlzheimer's Disease Neuroimaging Initiative. Individuals with mild cognitive impairment (MCI; n=179), individuals with AD (n=91), and normal controls (n=105). Neuropsychological tests, structural magnetic resonance imaging (MRI), amyloid-beta and tau in cerebrospinal fluid (CSF), and [18F]fluorodeoxyglucose positron emission tomography (FDG-PET) for the diagnosis of MCI or AD. MCI was defined according to subjective memory complaints corroborated by an informant and an abnormal score on the delayed paragraph recall subtest of the Wechsler Memory Scale-Revised, a Mini-Mental State Examination score greater than 23, and a Clinical Dementia Rating score of 0.5. Participants with AD satisfied National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria of probable AD. Neuropsychological tests and MRI were the most informative techniques, with 84% and 82% correct classifications, respectively, and areas under the receiver operating characteristic curve (AUCs) of 0.93 (90% confidence interval (CI)=0.91-0.95) and 0.88 (90% CI=0.85-0.91). FDG-PET and CSF assessments had 76% and 73% correct classifications, respectively, (AUC=0.77, 90% CI=0.71-0.83; AUC=0.77, 90% CI=0.73-0.82). These figures increased slightly when the techniques were combined. All analyses were repeated for the younger (<75) and older (≥75) halves of the sample. FDG-PET and CSF assessment were substantially less informative in the older cohort, and they did not add diagnostic information when all techniques were combined. Structural MRI and neuropsychological assessment are diagnostic methods of first choice if AD is suspected. CSF and FDG-PET add little to these diagnostic techniques, especially in older adults.

Proc Natl Acad Sci U S A. 2011 Sep 6;108(36):14968-73. Epub 2011 Aug 22.

Serotonin signaling is associated with lower amyloid- β levels and plaques in transgenic mice and humans.

Cirrito JR, Disabato BM, Restivo JL, Verges DK, Goebel WD, Sathyan A, Hayreh D, D'Angelo G, Benzinger T, Yoon H, Kim J, Morris JC, Mintun MA, Sheline YL.

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Aggregation of amyloid- β (A β) as toxic oligomers and amyloid plaques within the brain appears to be the pathogenic event that initiates Alzheimer's disease (AD) lesions. One therapeutic strategy has been to reduce A β levels to limit its accumulation. Activation of certain neurotransmitter receptors can regulate A β metabolism. We assessed the ability of serotonin signaling to alter brain A β levels and plaques in a mouse model of AD and in humans. In mice, brain interstitial fluid (ISF) A β levels were decreased by 25% following administration of several selective serotonin reuptake inhibitor (SSRI) antidepressant drugs. Similarly, direct infusion of serotonin into the hippocampus reduced ISF A β levels. Serotonin-dependent reductions in A β were reversed if mice were pretreated with inhibitors of the extracellular regulated kinase (ERK) signaling cascade. Chronic treatment with an SSRI, citalopram, caused a 50% reduction in brain plaque load in mice. To test whether serotonin signaling could impact A β plaques in humans, we retrospectively compared brain amyloid load in cognitively normal elderly participants who were exposed to antidepressant drugs within the past 5 y to participants who were not. Antidepressant-treated participants had significantly less amyloid load as quantified by positron emission tomography (PET) imaging with Pittsburgh Compound B (PiB). Cumulative time of antidepressant use within the 5-y period preceding the scan correlated with less plaque load. These data suggest that serotonin signaling was associated with less A β accumulation in cognitively normal individuals.

Neurology. 2011 Sep 6;77(10):951-8. Epub 2011 Aug 24.

Magnetic resonance spectroscopy, β -amyloid load, and cognition in a population-based sample of cognitively normal older adults.

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To determine the relationship between proton magnetic resonance spectroscopy (^1H MRS) metabolites and β -amyloid (A β) load and the effects of A β load on the association between ^1H MRS metabolites and cognitive function in cognitively normal older adults. We studied 311 cognitively normal older adults who participated in the population-based Mayo Clinic Study of Aging from January 2009 through September 2010. Participants underwent ^{11}C -Pittsburgh compound B (PiB) PET, ^1H MRS from the posterior cingulate gyri, and neuropsychometric testing to assess memory, attention/executive, language, and visual-spatial domain functions within 6 months. Partial Spearman rank order correlations were adjusted for age, sex, and education. Higher PiB retention was associated with abnormal elevations in myoinositol (mI)/creatinine (Cr) (partial $r(s) = 0.17$; $p = 0.003$) and choline (Cho)/Cr (partial $r(s) = 0.13$; $p = 0.022$) ratios. Higher Cho/Cr was associated with worse performance on Auditory Verbal Learning Test Delayed Recall (partial $r(s) = -0.12$; $p = 0.04$), Trail Making Test Part B (partial $r(s) = 0.12$; $p = 0.04$), Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol (partial $r(s) = -0.18$; $p < 0.01$), and WAIS-R Block Design (partial $r(s) = -0.12$; $p = 0.03$). Associations between ^1H MRS metabolites and cognitive function were not different among participants with high vs low PiB retention. In cognitively normal older adults, the ^1H MRS metabolite ratios mI/Cr and Cho/Cr are associated with the preclinical pathologic processes in the Alzheimer disease cascade. Higher Cho/Cr is associated with worse performance on domain-specific cognitive tests independent of A β load, suggesting that Cho/Cr elevation may also be dependent on other preclinical dementia pathologies characterized by Cho/Cr elevation such as Lewy body or ischemic vascular disease in addition to A β load.

Neurology. 2011 Aug 23;77(8):e47.

Teaching NeuroImages: Brain MRI and FDG-PET in malformations of cortical development and hippocampal hypoplasia.

Renard D, Castelnovo G, Daubin D, Collombier L, Briere C, Labauge P.

Source

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Neurology

Neurobiol Aging. 2011 Aug 18. [Epub ahead of print]

Posterior cingulate atrophy and metabolic decline in early stage Alzheimer's disease.

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To test the hypothesis that Alzheimer's disease (AD) patients with posterior cingulate/precuneus (PCP) atrophy would be a distinct disease form in view of metabolic decline. Eighty-one AD patients underwent (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and structural magnetic resonance imaging (MRI). Positron emission tomography and voxel-based morphometry (VBM) Z-score maps were generated for the individual patients using age-specific normal databases. The patients were classified into 3 groups based on atrophic patterns (no-Hipp-PCP, atrophy in neither hippocampus nor PCP; Hipp, hippocampal atrophy; PCP, PCP atrophy). There were 16 patients classified as no-Hipp-PCP, 55 as Hipp, and 10 as PCP. The Mini Mental State Examination (MMSE) score was similar among the groups. The greater FDG decline than atrophy was observed in all groups, including the no-Hipp-PCP. The PCP group was younger, and was associated with a greater degree of FDG decline in PCP than the others. There are diverse atrophic patterns in a spectrum of AD. In particular, a subset of patients show PCP atrophy, which is associated with greater metabolic burden.

Stroke. 2011 Aug 18. [Epub ahead of print]

Microembolism Versus Hemodynamic Impairment in Rosary-Like Deep Watershed Infarcts: A Combined Positron Emission Tomography and Transcranial Doppler Study.

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Deep watershed infarcts are frequent in high-grade carotid disease and are thought to result from hemodynamic impairment, particularly when adopting a rosary-like pattern. However, a role for microembolism has also been suggested, though never directly tested. Here, we studied the relationships among microembolic signals (MES) on transcranial Doppler, rosary-like deep watershed infarcts on brain imaging, and cerebral hemodynamic compromise on positron emission tomography (PET), all in severe symptomatic carotid disease. We hypothesized that rosary-like infarcts would be significantly associated with worse hemodynamic status, independent of the presence of MES. Sixteen patients with $\geq 70\%$ carotid disease ipsilateral to recent transient ischemic attack/minor stroke underwent magnetic resonance imaging including diffusion-weighted imaging, (15)O-PET, and transcranial Doppler. Mean transit time, a specific marker for hemodynamic impairment, was obtained in the symptomatic and unaffected hemispheres. Eleven of 16 patients had rosary-like infarcts (Rosary+) and 8 patients had MES. Mean transit time was significantly higher ($P=0.008$) in Rosary+ patients than in healthy controls ($n=10$), and prevalence of MES was not different between Rosary+ and Rosary- patients. Contrary to our hypothesis, however, the presence of MES within the Rosary+ subset was associated ($P=0.03$) with a better hemodynamic status than in their absence, with a significant ($P=0.02$) negative correlation between mean transit time and rate of MES/h. Contrary to mainstream understanding, rosary-like infarcts were not independent of presence and rate of MES, suggesting that microembolism plays a role in their pathogenesis, probably in association with hemodynamic impairment. Pending confirmation in a larger sample, these findings have management implications for patients with carotid disease and rosary-like infarcts.

Epilepsy Behav. 2011 Aug 16. [Epub ahead of print]

Brain damage and IQ in unilateral Sturge-Weber syndrome: Support for a "fresh start" hypothesis.

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We tested the hypothesis that extent of severe hypometabolism measured by fluorodeoxyglucose PET has a U-shaped (nonlinear) relationship to IQ in children with unilateral Sturge-Weber syndrome. Thirty-five consecutive children (age range: 30-153 months) with Sturge-Weber syndrome and unilateral brain involvement were enrolled in the study. Participants underwent cognitive assessment and interictal fluorodeoxyglucose PET scans. Regression analyses tested whether a quadratic model best accounted for the relationship between extent of severe cortical hypometabolism and IQ, controlling for seizure variables. A significant quadratic relationship was found between IQ and extent of severe (but not total) hypometabolism. Seizure variables also contributed significant variance to cognitive functions. Results suggest that intermediate size of severe hemispheric hypometabolism is associated with the worst cognitive outcomes, and small or absent lesions, with the best cognitive outcomes. Children in whom a very large extent of the hemisphere is severely affected are likely to have relatively preserved cognitive function.

Neurology

Neurology. 2011 Aug 30;77(9):904-10. Epub 2011 Aug 17.

Converging PET and fMRI evidence for a common area involved in human focal epilepsies.

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Experiments in animal models have identified specific subcortical anatomic circuits, which are critically involved in the pathogenesis and control of seizure activity. However, whether such anatomic substrates also exist in human epilepsy is not known. We studied 2 separate groups of patients with focal epilepsies arising from any cortical location using either simultaneous EEG-fMRI (n = 19 patients) or [(11)C]flumazenil PET (n = 18). Time-locked with the interictal epileptiform discharges, we found significant hemodynamic increases common to all patients near the frontal piriform cortex ipsilateral to the presumed cortical focus. GABA(A) receptor binding in the same area was reduced in patients with more frequent seizures. Our findings of cerebral blood flow and GABAergic changes, irrespective of where interictal or ictal activity occurs in the cortex, suggest that this area of the human primary olfactory cortex may be an attractive new target for epilepsy therapy, including neurosurgery, electrical stimulation, and focal drug delivery.

Dement Geriatr Cogn Disord. 2011 Aug 13;32(1):45-54. [Epub ahead of print]

Clinical Course of Patients with Familial Early-Onset Alzheimer's Disease Potentially Lacking Senile Plaques Bearing the E693A Mutation in Amyloid Precursor Protein.

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Background/Aims: Oligomeric amyloid β (A β) is currently considered to induce Alzheimer's disease (AD). We examined 2 patients with familial AD who possessed the Osaka (E693A) mutation in amyloid precursor protein. To the best of our knowledge, these patients are the first AD cases presumably affected with A β oligomers in the absence of senile plaques, and they support the A β oligomer hypothesis. Methods: We evaluated the clinical course, neuropsychological data, cerebrospinal fluid biomarker levels, magnetic resonance imaging (MRI) scans, fluorodeoxyglucose-positron emission tomography (PET) scans, and Pittsburgh compound B (PiB)-PET images of these patients. Results: In the early stages, these patients developed memory disturbances in a similar rate to patients with sporadic AD. Despite their memory disturbances, both patients showed only limited brain atrophy on MRI and little amyloid accumulation on PiB-PET. Subsequent to the development of memory disturbances, both patients suffered from motor dysfunction, probably due to cerebellar ataxia, and, within a few years, the patients fell into an apallic state. Conclusions: Familial AD patients with Osaka (E693A) mutation show severe dementia, cerebellar ataxia, and gait disturbances.

Clin Cancer Res. 2011 Aug 15. [Epub ahead of print]

Metabolic Imaging: A link between Lactate Dehydrogenase A, Lactate and Tumor Phenotype.

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We compared the metabolic profiles and the association between LDH-A expression and lactate production in two isogenic murine breast cancer cell lines and tumors (67NR and 4T1). These cell lines were derived from a single mammary tumor and have different growth and metabolic phenotypes. LDH-A expression, lactate concentration, glucose utilization and oxygen consumption were measured in cells, and the potential relationship between tumor lactate levels (measured by magnetic resonance spectroscopic imaging (MRSI)) and tumor glucose utilization (measured by [18F] 2-deoxy-2-fluoro-D-glucose positron emission tomography ([18F]FDG-PET)) was assessed in orthotopic breast tumors derived from these cell lines. We show a substantial difference in LDH-A expression between 67NR and 4T1 cells under normoxia and hypoxia. We also show that small orthotopic 4T1 tumors generate ten-fold more lactate than corresponding 67NR tumors. The high lactate levels in small primary 4T1 tumors are associated with intense pimonidazole staining (a hypoxia indicator). Less intense hypoxia staining was observed in the larger 67NR tumors, and is consistent with the gradual increase and plateau of lactate concentration in enlarging 67NR tumors. Lactate-MRSI has a greater dynamic range than [18F]FDG-PET and may be a more sensitive measure with which to evaluate the aggressive and metastatic potential of primary breast tumors.

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Bipolar Disord. 2011 Jun;13(4):406-13. doi: 10.1111/j.1399-5618.2011.00936.x.

Striatal dopamine transporter availability in unmedicated bipolar disorder.

Anand A, Barkay G, Dzemidzic M, Albrecht D, Karne H, Zheng QH, Hutchins GD, Normandin MD, Yoder KK.

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Anand A, Barkay G, Dzemidzic M, Albrecht D, Karne H, Zheng Q-H, Hutchins GD, Normandin MD, Yoder KK. Striatal dopamine transporter availability in unmedicated bipolar disorder. *Bipolar Disord* 2011; 13: 406-413. © 2011 The Authors. Journal compilation © 2011 John Wiley & Sons A/S. Objectives: Dopamine transmission abnormalities have been implicated in the etiology of bipolar disorder (BPD). However, there is a paucity of receptor imaging studies in BPD, and little information is available about the dopamine system in BPD. Reuptake of synaptic dopamine by the dopamine transporter (DAT) is the principal mechanism regulating dopamine neurotransmission, and is often used as a marker for presynaptic dopamine function. This positron emission tomography (PET) study investigated whether DAT availability differed between BPD and healthy control subjects. Methods: A total of 11 unmedicated BPD patients in either the euthymic or depressed phase and 13 closely matched healthy subjects underwent PET imaging with the DAT-selective radiotracer [(11)C]CFT and a structural magnetic resonance imaging (MRI) scan. Striatal binding potential (BP(ND)) was estimated using the multilinear reference tissue model. Region of interest and analyses were conducted to test for differences in [(11)C]CFT BP(ND) between groups. Results: Unmedicated BPD subjects had significantly lower DAT availability relative to healthy controls in bilateral dorsal caudate. Conclusions: The results of this study support the hypothesis that there are abnormalities in the dopaminergic system in BPD, and suggest that DAT availability may be related to the neuropathology of BPD. Future studies are needed to determine if DAT availability cycles with disease phase.

Am J Geriatr Psychiatry. 2011 Aug 11. [Epub ahead of print]

Serotonin Transporter Occupancy and the Functional Neuroanatomic Effects of Citalopram in Geriatric Depression.

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The functional neuroanatomic changes associated with selective serotonin reuptake inhibitor (SSRI) treatment have been the focus of positron emission tomography (PET) studies of cerebral glucose metabolism in geriatric depression. To evaluate the underlying neurochemical mechanisms, both cerebral glucose metabolism and serotonin transporter (SERT) availability were measured before and during treatment with the SSRI, citalopram. It was hypothesized that SERT occupancy would be observed in cortical and limbic brain regions that have shown metabolic effects, as well as striatal and thalamic regions that have been implicated in prior studies in midlife patients. Psychiatric outpatient clinic. Seven depressed patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for current major depressive episode were enrolled. Patients underwent a 12-week open-label trial of the SSRI, citalopram. Patients underwent high-resolution research tomography PET scans to measure changes in cerebral glucose metabolism and SERT occupancy by citalopram treatment (after 8-10 weeks of treatment). Three different tracer kinetic models were applied to the [C]-DASB region-of-interest data and yielded similar results of an average of greater than 70% SERT occupancy in the striatum and thalamus during citalopram treatment. Voxel-wise analyses showed significant SERT occupancy in these regions, as well as cortical (e.g., anterior cingulate, superior and middle frontal, precuneus, and limbic (parahippocampal gyrus) areas that also showed reductions in glucose metabolism. The findings suggest that cortical and limbic SERT occupancy may be an underlying mechanism for the regional cerebral metabolic effects of citalopram in geriatric depression.

Seizure. 2011 Aug 6. [Epub ahead of print]

Evaluating the feasibility of measures of motor threshold and cortical silent period as predictors of outcome after temporal lobe epilepsy surgery.

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Although it is well known that ES alters cortical excitability, little is known about the relationship between ES outcome and cortical excitability. Transcranial magnetic stimulation has been successfully used to evaluate cortical excitability in epilepsy patients. The present study aimed to assess the value of the motor threshold (MT) and cortical silent period (CSP) as predictors of the outcome of temporal lobe epilepsy surgery (TLES). Epileptic foci in the epilepsy patients were identified via video-electroencephalography (v-EEG) monitoring, brain magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT), and positron emission tomography (PET), and neurophysiological testing. MT, CSP-150, and CSP-max were measured in 10 epilepsy patients on both the ipsilateral and contralateral side of the epileptic focus 1 week before and 3 months after TLES. Pre- and post-operative MT and CSP measurements were compared, and the results were interpreted

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based on the clinical outcome of TLES. Mean follow-up period was 28.8 months. In all, 8 patients were seizure-free post TLES, whereas in 2 patients seizures persisted. No significant differences were observed in ipsilateral or contralateral hemisphere MT measurements before and after surgery. Both CSP-150 and CSP-max values in the non-focal hemispheres decreased in the 8 patients that were seizure-free post TLES, whereas no differences were observed in the 2 patients with seizures that persisted post TLES. The present findings indicate that monitoring pre- and post-TLES CSP changes may be predictive of the early clinical outcome of TLES.

Rinsho Shinkeigaku. 2011 Jul;51(7):487-92.

[A case of Castleman disease with status epileptics originating from focal cortical dysplasia].

[Article in Japanese]

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A 55-year-old man was admitted to our hospital because of prolonged consciousness disturbance after generalized convulsions. He had been afflicted with chronic inflammatory symptoms since 43 years of age, while multiple abdominal lymphadenopathy with a high level of serum IL-6 was revealed at the age of 53. FDG-PET/CT showed hypermetabolism in the left medial portion of the frontal lobe. Biopsy specimens of this lesion revealed a pathology of focal cortical dysplasia (FCD). Non-convulsive status epileptics continued despite enhanced treatment with antiepileptic drugs, while cortical T2 hyperintense lesions developed and expanded. Castleman disease was confirmed by pathological findings of abdominal lymph node biopsy specimens. The patient showed a higher level of IL-6 in cerebrospinal fluid (1,400 pg/dl) than in serum (720 pg/dl), thus indicating intrathecal production of this proinflammatory cytokine. We concluded that continuous exposure of FCD tissue to IL-6 may have augmented epileptogenesis of the originally silent congenital lesion.

Curr Opin Neurol. 2011 Oct;24(5):504-10.

Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations.

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Recent progress in serological screening for paraneoplastic autoantibodies and diagnostic imaging techniques to detect malignancies has resulted in a broadening of the concept of paraneoplastic neurologic syndromes through the characterization of nonclassical clinical features. The goal of this article was to review the recent literature describing the wide-ranging clinicopathological manifestations of paraneoplastic neuropathy. The classical feature of paraneoplastic neuropathy is subacute sensory neuronopathy; in addition, sensorimotor neuropathies, such as Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, brachial plexopathy, and vasculitic neuropathy, are sometimes observed. Some studies also describe the occurrence of autonomic neuropathies, including autoimmune autonomic ganglionopathy and chronic gastrointestinal pseudo-obstruction. Whole-body fluorodeoxyglucose positron emission tomography (FDG-PET) or FDG-PET/computed tomography may be helpful to detect malignancies that cannot be detected by conventional screening tests. The presence of paraneoplastic neuropathy should be considered in all patients with malignancy and can occur at any point in the disease, even during or after chemotherapy, radiation, or stem cell transplantation. The presence of paraneoplastic autoantibodies, especially anti-Hu and anti-CV2/CRMP-5 antibodies, may support the diagnosis of paraneoplastic neuropathy. Immunomodulatory treatment before, during, or after antineoplastic therapy may be of benefit for patients with paraneoplastic neuropathy and has been used even when the underlying malignancy cannot be identified. Recognition of the variable manifestations of paraneoplastic neuropathy is important, as diagnosis at an earlier stage facilitates prompt treatment and provides better chances of good outcomes.

Neuropsychiatr Dis Treat. 2011;7:415-24. Epub 2011 Jul 13.

Open-label study of the short-term effects of memantine on FDG-PET in frontotemporal dementia.

Chow TW, Graff-Guerrero A, Verhoeff NP, Binns MA, Tang-Wai DF, Freedman M, Masellis M, Black SE, Wilson AA, Houle S, Pollock BG.

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Memantine has shown effects on cortical metabolism in Alzheimer's disease (AD), and the mechanism of action may not be specific to AD alone. We hypothesized that participants with frontotemporal dementia taking memantine would show an increased cortical metabolic activity in frontal regions, temporal regions, or in salience network hubs. Sixteen participants with behavioral or language variant frontotemporal dementia syndromes (FTD) were recruited from tertiary FTD clinics and treated with memantine hydrochloride 10 mg twice daily in this fixed-dose, open-label pilot study. The primary endpoint was enhancement of cortical metabolic activity after 7-8 weeks of treatment. Secondary endpoints were measures of mood and behavior disturbance, frontal executive function, and motor disturbance. Voxel-wise parametric image analysis of positron emission tomography (PET) data from seven behavioral variant FTD patients, eight semantic dementia patients, and one progressive nonfluent

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aphasia patient, of mean age 64.3 years, mean duration of illness 4.25 years, and baseline mean sum of boxes Clinical Dementia Rating score 6.59, revealed an increase in [(18)F]-fluorodeoxyglucose (FDG) normalized metabolic activity in bilateral insulae and the left orbitofrontal cortex ($P < 0.01$). The increase on FDG-PET did not correlate with changes on behavioral inventories. Post hoc analysis indicated that semantic dementia participants drove this finding. This open-label clinical PET study suggests that memantine induces an increase in metabolism in the salience network in FTD. A placebo-controlled follow-up study is warranted.

Epilepsia. 2011 Sep;52(9):1725-32. doi: 10.1111/j.1528-1167.2011.03172.x. Epub 2011 Jul 19.

Functional neuroimaging in startle epilepsy: Involvement of a mesial frontoparietal network.

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Purpose: Startle epilepsy is a rare form of epilepsy with seizures triggered by unexpected stimuli. Previous studies have suggested the participation of several brain regions, such as the supplementary motor area (SMA) or the mesial aspect of the frontal and parietal lobes in the generation of startle epilepsy. However, how these brain regions interact with each other during seizures remains largely unknown. The aim of this study was to get insight into brain structures involved in startle-induced seizures using an approach with functional neuroimaging. **Methods:** Four patients with startle epilepsy secondary to unexpected sounds were studied. All of them underwent a presurgical evaluation including ictal-single-emission computed tomography/subtraction ictal SPECT coregistered to MRI (magnetic resonance imaging) (SPECT/SISCOM). We searched for areas with ictal changes of perfusion higher than two standard deviations (2 SD) above the reference. In one patient, a fluorodeoxyglucose-positron emission tomography (FDG-PET) and an ictal electroencephalography-functional MRI (EEG-fMRI) were also performed. In this patient, the results of FDG-PET and sequential analysis of EEG-fMRI were compared to SISCOM. **Key Findings:** All the patients had their typical startle-induced seizures, consistent with bilateral asymmetric tonic seizures. Ictal-EEG pattern was located over the mesial centroparietal region in all of them. In three of four patients, a significant hyperperfusion over the mesial frontocentral region was seen, involving the SMA, the perirolandic region, and the precuneus. In one patient, who had a congenital bilateral perisylvian polymicrogyria, it was located over the lateral perirolandic region. 18F-FDG-PET results in the patient in whom it was done, were concordant with SISCOM findings. Ictal EEG-fMRI showed an initial activation located over the precuneus, SMA, cingulate gyrus, and the precentral/perirolandic area. **Significance:** By using a functional neuroimaging approach we have found that startle-induced seizures could be generated by the interaction of a frontoparietal network located over the mesial surface of the brain.

Seizure. 2011 Jul 16. [Epub ahead of print]

Temporo-spatial analyses define epileptogenic and functional zones in a case of Dyke-Davidoff-Masson syndrome.

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Dyke-Davidoff-Masson syndrome (DDMS) is a rare epilepsy syndrome that is characterized by cerebral hemiatrophy, homolateral skull hyperplasia, hyperpneumatization of the paranasal sinuses, seizures with or without mental retardation, and contralateral hemiparesis. We describe a case of DDMS in a 40-year-old female who had complex partial seizures with occasional secondary generalization since the age of 4 years. Her seizure frequency was 10-20 seizures/month even though she took four antiepileptic drugs. We applied magnetic resonance imaging (MRI), positron emission tomography (PET), functional MRI, and invasive electroencephalography (EEG) to define her epileptogenic and functional zones. Brain MRI showed prominent atrophy in the left frontal dorsal and lateral regions and mild atrophy of the left superior temporal gyrus and left parietal gyri. Interictal PET revealed decreased glucose metabolism in the atrophic regions. Functional MRI demonstrated that the inferior frontal and inferior parieto-occipital regions of the right hemisphere were activated by language testing. Invasive EEG revealed that the left lateral temporal lobe was the sole source of her seizures. Our results imply that the "metabolic border zone" rather than the atrophic region plays an important role in seizure activity, and that reorganization of functional zones occur after cerebral damage early in life.

J Neurol Sci. 2011 Jul 13. [Epub ahead of print]

Neural reward processing under dopamine agonists: Imaging.

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Impulse control disorders (ICDs) are increasingly reported as a considerable side-effect of treatment with dopaminergic medication (both levodopa and dopamine agonists (DA)). ICDs together with punding are described within the entity of dopamine dysregulation syndrome along

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with immediate reward seeking and addictive behaviors. The brain functions involved in reward processing in general and their modulation by medication can be characterized by neuropsychological assessments and underlying neurobiology can be investigated by functional neuroimaging techniques such as functional magnetic resonance imaging (fMRI) or positron emission tomography (PET). By this approach, functional changes of brain areas involved in reward processing under short-term or chronic DA therapy were studied. Functional changes in a network involving striatal-thalamic loops, key structures of the reward system, together with limbic areas (such as the amygdala) and the ventral tegmental area could be related to pharmacological alterations of reward processing by dopaminergic medication. In particular, altered ventral striatal functioning seems to relate to ICDs such as pathological gambling. A general medication effect in patients under DA in terms of a sensitization toward ICD could be demonstrated. A synopsis is given on the applications of functional neuroimaging to investigate reward processing and the influence of dopaminergic medication.

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FDG-PET hypermetabolism in paraneoplastic cerebellar degeneration.

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Arch Neurol. 2011 Jul 11. [Epub ahead of print]

Using Positron Emission Tomography and Florbetapir F 18 to Image Cortical Amyloid in Patients With Mild Cognitive Impairment or Dementia Due to Alzheimer Disease.

Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, Joshi AD, Clark CM, Mintun MA, Pontecorvo MJ, Doraiswamy PM, Johnson KA, Skovronsky DM, Reiman EM.

Chen, Ayutyanont, and Reiman, Ms Liu, and Messrs Roontiva and Thiyyagura, Arizona Alzheimer's Consortium (Drs Fleisher, Chen, and Reiman), Department of Psychiatry, University of Arizona College of Medicine (Dr Reiman), Neurogenomics Division, Translational Genomics Research Institute, Phoenix (Dr Reiman), and Department of Mathematics, Arizona State University, Tempe (Dr Chen); Department of Neurosciences, University of California, San Diego (Dr Fleisher); Avid Radiopharmaceuticals (Drs Clark, Mintun, Pontecorvo, and Skovronsky and Mr Joshi) and University of Pennsylvania School of Medicine, Philadelphia (Drs Clark and Skovronsky); Washington University School of Medicine, St Louis, Missouri (Dr Mintun); Department of Neurology, Brigham and Women's Hospital, Harvard Medical School, and Departments of Neurology and Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (Dr Johnson); and Departments of Psychiatry, Duke University Medical Center, Durham, North Carolina (Dr Doraiswamy).

To characterize quantitative florbetapir F 18 (hereafter referred to as simply florbetapir) positron emission tomographic (PET) measurements of fibrillar β -amyloid (A β) burden in a large clinical cohort of participants with probable Alzheimer disease (AD) or mild cognitive impairment (MCI) and older healthy controls (OHCs). Cerebral-to-whole-cerebellar florbetapir standard uptake value ratios (SUVRs) were computed. Mean cortical SUVRs were compared. A threshold of SUVRs greater than or equal to 1.17 was used to reflect pathological levels of amyloid associated with AD based on separate antemortem PET and postmortem neuropathology data from 19 end-of-life patients. Similarly, a threshold of SUVRs greater than 1.08 was used to signify the presence of any identifiable A β because this was the upper limit from a separate set of 46 individuals 18 to 40 years of age who did not carry apolipoprotein E (APOE) ϵ 4. Multiple research imaging centers. A total of 68 participants with probable AD, 60 participants with MCI, and 82 OHCs who were 55 years of age or older. Main Outcome Measure Florbetapir-PET activity. All of the participants (ie, those with probable AD or MCI and those who were OHCs) differed significantly in mean (SD) cortical florbetapir SUVRs (1.39 [0.24], 1.17 [0.27], and 1.05 [0.16], respectively; $P < 1.0 \times 10^{-7}$), in percentage meeting levels of amyloid associated with AD by SUVR criteria (80.9%, 40.0%, and 20.7%, respectively; $P < 1.0 \times 10^{-7}$), and in percentage meeting SUVR criteria for the presence of any identifiable A β (85.3%, 46.6%, and 28.1%, respectively; $P < 1.0 \times 10^{-7}$). Among OHCs, the percentage of florbetapir positivity increased linearly by age decile ($P = .05$). For the 54 OHCs with available APOE genotypes, APOE ϵ 4 carriers had a higher mean (SD) cortical SUVR than did noncarriers (1.14 [0.2] vs 1.03 [0.16]; $P = .048$). The findings of our analysis confirm the ability of florbetapir-PET SUVRs to characterize amyloid levels in clinically probable AD, MCI, and OHC groups using continuous and binary measures of fibrillar A β burden. It introduces criteria to determine whether an image is associated with an intermediate-to-high likelihood of pathologic AD or with having any identifiable cortical amyloid level above that seen in low-risk young controls.

Arch Neurol. 2011 Jul 11. [Epub ahead of print]

Association Between In Vivo Fluorine 18-Labeled Flutemetamol Amyloid Positron Emission Tomography Imaging and In Vivo Cerebral Cortical Histopathology.

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To determine the correspondence of in vivo quantitative estimates of brain uptake of fluorine 18-labeled flutemetamol with immunohistochemical estimates of amyloid levels in patients who underwent previous biopsy. Cross-sectional study of (18)F-flutemetamol positron emission tomography (PET) findings in patients with prior cortical biopsy specimen stained for the presence or absence of amyloid plaques. University hospital. Patients Seven patients who previously had a prior right frontal cortical biopsy at the site of ventriculoperitoneal placement for presumed normal pressure hydrocephalus were recruited. Inclusion criteria included an adequate biopsy specimen for detection and quantification of β -amyloid pathology and age older than 50 years. Intervention All patients underwent an (18)F-flutemetamol PET scan. Quantitative measures of (18)F-flutemetamol uptake (standardized uptake value ratio, a ratio of mean target cortex activity divided by that in a cerebellar reference region) were made at a location contralateral to the biopsy site and compared with estimates of amyloid load based on immunohistochemical and histological staining. There was complete agreement between visual reads of (18)F-flutemetamol PET scans (3 blinded readers with majority rule) and histology. A regression model, including time from biopsy as a covariate, demonstrated a significant relationship ($P = .01$) between (18)F-flutemetamol uptake and percentage of area of amyloid measured by a monoclonal antibody raised against amyloid (NAB228). Similar results were found with the amyloid-specific monoclonal antibody 4G8 and Thioflavin S. To our knowledge, these data are the first to demonstrate the concordance of (18)F-flutemetamol PET imaging with histopathology, supporting its sensitivity to detect amyloid and potential use in the study and detection of Alzheimer disease.

Neurosci Lett. 2011 Aug 21;501(1):35-40. Epub 2011 Jun 29.

Changes in cerebral glucose metabolism in patients with mild-to-moderate Alzheimer's disease: A pilot study with the Chinese herbal medicine fuzhisan.

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The aim of this study was to investigate the effects of fuzhisan (FZS, 10mg/day), a Chinese herbal medicine, on cerebral glucose metabolism and neuropsychological metrics in patients with mild-to-moderate Alzheimer's disease (AD). This was a 12-week, randomized, double-blind, placebo-controlled pilot study. Twenty-two subjects were randomly assigned to groups that received FZS ($n=12$) or placebo ($n=10$). Positron emission tomography (PET) was used to study the regional cerebral metabolic rate of glucose consumption (rCMRglc) at baseline and week 12. We evaluated the clinical efficacy of FZS on cognition and behavioral functions using the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) and the Neuropsychiatric Index (NPI), respectively. Compared with placebo, FZS significantly improved ADAS-Cog scores and NPI scores at week 12. Moreover, FZS treatment favorably improved rCMRglc in the bilateral temporal and parietal cortices, hippocampus, and posterior cingulate gyrus. These results suggest that FZS treatment may have a positive effect on cognition, behavioral functions, and rCMRglc in mild-to-moderate AD patients.

Clin Nucl Med. 2011 Aug;36(8):725-7.

Cerebral hypermetabolism demonstrated by FDG PET in familial Creutzfeldt-Jakob disease.

Nagasaka T, Nagasaka K, Ohta E, Shindo K, Takiyama Y, Shiozawa Z, Miyazawa N, Yamasaki N, Mori N, Onda H, Shinohara T.

Source

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Right cerebral and contralateral cerebellar hypermetabolism were observed on FDG PET in a 68-year-old woman with familial Creutzfeldt-Jakob disease (CJD) at an early stage before seizures occurred. The disease progressed with frequent seizures, myoclonus, and a startle reaction. In all past reports, FDG PET studies demonstrated hypometabolism in the cerebrum, cerebellum, and thalamus in patients with CJD. Focal hypermetabolism corresponding with epileptic foci is a common finding in ictal epilepsy patients, and hypometabolism is common in patients with myoclonus or the startle reaction. This finding may reflect a prodromal pathophysiology of epilepsy. Attention should be paid to the diagnosis of CJD while using FDG PET.

Neurology. 2011 Jul 12;77(2):125-31. Epub 2011 Jun 29.

Plasma A β and PET PiB binding are inversely related in mild cognitive impairment.

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To evaluate the relations between PET Pittsburgh compound B (PiB-PET) binding (amyloid imaging) and plasma A β in patients with mild cognitive impairment (MCI) and similarly aged controls. In 20 patients with MCI and 19 cognitively intact controls (case-control study), PiB binding potential (BP(nd)) was assessed in 4 regions, and total brain excluding cerebellum, referenced to cerebellar binding. The mean of plasma A β levels measured in duplicate was analyzed. Plasma A β 42/A β 40 ratio was decreased in MCI compared to controls (mean 0.15 SD 0.04 vs mean 0.19 SD 0.07, $p = 0.03$) but A β 40 ($p = 0.3$) and A β 42 ($p = 0.06$) levels did not differ between the 2 groups. PiB BP(nd) was increased in MCI compared to controls in the cingulate ($p = 0.02$), parietal ($p = 0.02$), and total brain ($p = 0.03$), but not in prefrontal cortex ($p = 0.08$) or parahippocampal gyrus ($p = 0.07$). Linear regression analyses adjusting for age, sex, and cognitive test scores showed that low A β 42/A β 40 ratio was associated with high cingulate, parietal, and total brain PiB binding ($0.01 < p \leq 0.05$). These associations between PiB binding and the A β 42/A β 40 ratio were strongest in PiB-positive subjects and within the MCI group. Though cross-sectional, the findings support the "sink" hypothesis that increased brain A β is accompanied by lower peripheral levels of A β , particularly the A β 42/A β 40 ratio in patients with MCI. The association between PiB binding and the plasma A β 42/A β 40 ratio suggests possible use of plasma A β combined with PiB binding as a risk biomarker with potential clinical application.

Neurology. 2011 Jul 5;77(1):48-54. Epub 2011 Jun 22.

Cerebral microhemorrhage and brain β -amyloid in aging and Alzheimer disease.

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Incidental cerebral microhemorrhage (MH) is frequently found in older individuals scanned with susceptibility-weighted MRI (SWI) or gradient-recalled echo MRI. MH have been linked with β -amyloid (A β) deposition using (11)C-Pittsburgh compound B (PiB) PET in Alzheimer disease (AD) and cerebral amyloid angiopathy (CAA). We hypothesized that A β deposition in asymptomatic elderly individuals is associated with lobar MH (LMH). This was a cross-sectional study of 84 elderly healthy controls (HC), 28 subjects with mild cognitive impairment (MCI), and 26 subjects with probable AD who underwent 3-T SWI and (11)C-PiB PET. (11)C-PiB cortical binding was quantified normalized to cerebellar cortex (standardized uptake value ratio [SUVR]) and scans classified as positive (PiB+) or negative (PiB-) by visual inspection. MH were manually counted and categorized by region and as lobar or nonlobar. LMH were present in 30.8% of AD, 35.7% of MCI, and 19.1% of HC. The prevalence of LMH among PiB+ subjects was similar, regardless of clinical classification (AD 30.8%, MCI 38.9%, HC 41.4%, $p > 0.7$). HC with LMH had significantly higher mean neocortical SUVR (1.7 ± 0.5) than HC without LMH (1.3 ± 0.3 , $p = 0.01$). In HC, there was a positive correlation between number of LMH and SUVR, and between LMH and age. In HC, PiB+ (odds ratio [OR] 7.3, 95% confidence interval [CI] 1.6-33.7, $p = 0.01$) and age (OR 1.2, 95% CI 1.03-1.3, $p = 0.02$) both independently predicted the occurrence of LMH using logistic regression. Asymptomatic A β deposition in older adults is strongly associated with LMH.

Neurology. 2011 Jul 5;77(1):39-47. Epub 2011 Jun 22.

Precuneus amyloid burden is associated with reduced cholinergic activity in Alzheimer disease.

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This study examined the relationship between postmortem precuneus cholinergic enzyme activity, Pittsburgh compound B (PiB) binding, and soluble amyloid- β concentration in mild cognitive impairment (MCI) and Alzheimer disease (AD). Choline acetyltransferase (ChAT) activity, [(3)H]PiB binding, and soluble amyloid- β (1-42) (A β 42) concentration were quantified in precuneus tissue samples harvested postmortem from subjects with no cognitive impairment (NCI), MCI, and mild AD and correlated with their last antemortem Mini-Mental State Examination (MMSE) score and postmortem pathologic evaluation according to the National Institute on Aging-Reagan criteria, recommendations of the Consortium to Establish a Registry for Alzheimer's Disease, and Braak stage. Precuneus ChAT activity was lower in AD than in NCI and was comparable between MCI and NCI. Precuneus [(3)H]PiB binding and soluble A β 42 levels were elevated in MCI and significantly higher in AD than in NCI. Across all case subjects, reduced ChAT activity was associated with increased [(3)H]PiB binding, increased soluble A β 42, lower MMSE score, presence of the APOE*4 allele, and more advanced AD pathology. Despite accumulating amyloid burden, cholinergic enzyme activity is stable in the precuneus during prodromal AD. A decline in precuneus ChAT activity occurs only in clinical AD, when PiB binding and soluble A β 42 levels are substantially elevated compared with those in MCI. Anti-amyloid interventions in MCI case subjects with a positive PiB PET scan may aid in reducing cholinergic deficits and cognitive decline later in the disease process.

Neurology. 2011 Aug 2;77(5):453-60. Epub 2011 Jun 22.

Early detection of Alzheimer disease: 11C-PiB PET in twins discordant for cognitive impairment.

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The aim of this study was to investigate whether cognitively preserved monozygotic or dizygotic cotwins of persons with Alzheimer disease (AD) exhibit increased brain amyloid accumulation. We performed a cross-sectional carbon-11 labeled 2-(4'-methylaminophenyl)-6-hydroxybenzothiazole ((11)C)-Pittsburgh compound B (PiB) PET study on 9 monozygotic and 8 dizygotic twin pairs discordant for cognitive impairment as well as on 9 healthy elderly control subjects. (11)C-PiB uptake was analyzed with Statistical Parametric Mapping and with region of interest analysis with the region-to-cerebellum ratio as a measure of tracer uptake. Cognitively preserved monozygotic cotwins of cognitively impaired probands had increased cortical (11)C-PiB uptake (117%-121% of control mean) in their temporal and parietal cortices and the posterior cingulate. Cognitively preserved dizygotic subjects did not differ from the controls. Further, the cognitively preserved monozygotic subjects showed similar (11)C-PiB uptake patterns as their cognitively impaired cotwins. The cognitively impaired subjects (monozygotic and dizygotic individuals combined) showed typical Alzheimer-like patterns of (11)C-PiB uptake. Genetic factors appear to influence the development of Alzheimer-like β -amyloid plaque pathology. The dissociation between cognitive impairment and brain β -amyloidosis in monozygotic twins implies that there may be important environmental/acquired factors that modulate the relationship between brain amyloidosis and neurodegeneration. AD may be detectable in high-risk individuals in its presymptomatic stage with (11)C-PiB PET, but clinical follow-up will be needed to confirm this.

J Clin Neurosci. 2011 Aug;18(8):1130-2. Epub 2011 Jun 22.

Hypermetabolism in the left thalamus and right inferior temporal area on positron emission tomography-statistical parametric mapping (PET-SPM) in a patient with Charles Bonnet syndrome resolving after treatment with valproic acid.

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Charles Bonnet syndrome (CBS) is characterized by the occurrence of complex visual hallucinations in visually impaired patients who understand that what they see is unreal. The pathophysiologic mechanism of CBS is poorly understood. However, hypermetabolism of the thalamocortical pathway as a result of deafferentation was recently proposed as a possible mechanism. A 69-year-old patient with CBS presented with a 5-year history of visual hallucinations after bilateral visual impairment, which had progressed to troublesome images of many unreal people and animals. Positron emission tomography-statistical parametric mapping (PET-SPM) imaging studies initially revealed hypermetabolism in the right inferior temporal area and left thalamus, which disappeared after treatment with valproic acid. This case, using PET-SPM analysis, supports the thalamic hypermetabolism theory of CBS.

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Effect of Illiteracy on Neuropsychological Tests and Glucose Metabolism of Brain in Later Life.

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The acquisition of literacy during childhood may affect the functional organization of the brain. We studied the effects of illiteracy on neuropsychological tests and brain glucose metabolism in later life. We recruited 12 illiterate elderly farmers who never attended school and acquired no knowledge of reading or writing. These illiterate subjects were compared with literate subjects in terms of neuropsychological performance and brain glucose metabolism. All subjects were over 65 years and had same socioeconomic environment and normal activities of daily living. Neuropsychological tests indicated that the performance of illiterate subjects was worse than that of literate subjects in all cognitive domains with the exception of forward digit span, tool-use and tool-free gestures, and verbal generation of grocery items. The SPM analysis showed that illiterate subjects had reduced FDG-uptake relative to literate subjects, predominantly in the rostral part of the left superior frontal gyrus and less strikingly in the left rectal gyrus, right cerebellar declive, and right cerebellar tonsil. In contrast, hypermetabolism was found only in the left precuneus. These results suggest that reading and writing during childhood is associated with activation of the frontal pole that may play a critical role in complex aspects of human cognition.

J Neurol Sci. 2011 Sep 15;308(1-2):1-8. Epub 2011 Jun 22.

Isolated intracranial Whipple's disease-Report of a rare case and review of the literature.

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Whipple's disease (WD) is a rare multisystemic infectious disease that can involve a variety of organs namely the gastrointestinal tract, lymphatic system, heart and nervous system. Myorhythmia is a hallmark of WD. Isolated CNS involvement is very rare. We present a 50year-old African-

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American woman with rapid cognitive decline, visual hallucinations, insomnia, dysarthria, and gait unsteadiness. She subsequently developed pendular nystagmus and gaze paresis. Serial brain MRI scans showed T2 hyperintense lesions in the left striatum and right parahippocampal gyrus. FDG-PET scan showed marked increase of glucose uptake in the left putamen. Serum and CSF PCR for *Tropheryma whipplei* was negative. Stereotactic biopsy of the lesion and tissue PCR was consistent with WD. REVIEW OF LITERATURE: A systematic review identified 24 cases of isolated intracranial presentation of WD since 1975. Cases with systemic and extracranial manifestations were excluded. In patients with rapidly progressive cognitive decline with negative workup for common etiologies, there should be a high index of suspicion for WD. Diagnosis of WD remains a challenge as traditional methods commonly fail to culture *T. whipplei*. PET scans can help in identifying areas of inflammation that can be biopsied. Our case proves that a negative serum and CSF PCR should not exclude CNS WD and a brain biopsy of the lesion with PCR assay should be performed when possible.

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Glucose metabolism in small subcortical structures in Parkinson's disease.

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Borghammer P, Hansen SB, Eggers C, Chakravarty M, Vang K, Aanerud J, Hilker R, Heiss W-Dieter, Rodell A, Munk OL, Keator D, Gjedde A. Glucose metabolism in small subcortical structures in Parkinson's disease. Acta Neurol Scand: DOI: 10.1111/j.1600-0404.2011.01556.x. © 2011 John Wiley & Sons A/S. Objectives - Evidence from experimental animal models of Parkinson's disease (PD) suggests a characteristic pattern of metabolic perturbation in discrete, very small basal ganglia structures. These structures are generally too small to allow valid investigation by conventional positron emission tomography (PET) cameras. However, the high-resolution research tomograph (HRRT) PET system has a resolution of 2 mm, sufficient for the investigation of important structures such as the pallidum and thalamic subnuclei. Materials and methods - Using the HRRT, we performed [(18)F]-fluorodeoxyglucose (FDG) scans on 21 patients with PD and 11 age-matched controls. We employed three types of normalization: white matter, global mean, and data-driven normalization. We performed volume-of-interest analyses of small subcortical gray matter structures. Voxel-based comparisons were performed to investigate the extent of cortical hypometabolism. Results - The most significant level of relative subcortical hypermetabolism was detected in the external pallidum (GPe), irrespective of normalization strategy. Hypermetabolism was suggested also in the internal pallidum, thalamic subnuclei, and the putamen. Widespread cortical hypometabolism was seen in a pattern very similar to previously reported patterns in patients with PD. Conclusion - The presence and extent of subcortical hypermetabolism in PD is dependent on type of normalization. However, the present findings suggest that PD, in addition to widespread cortical hypometabolism, is probably characterized by true hypermetabolism in the GPe. This finding was predicted by the animal 2-deoxyglucose autoradiography literature, in which high-magnitude hypermetabolism was also most robustly detected in the GPe.

Neuropsychologia. 2011 Jul;49(9):2776-83. Epub 2011 Jun 12.

Face-name associative memory performance is related to amyloid burden in normal elderly.

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Cerebral amyloid beta (A β) deposition occurs in a substantial fraction of cognitively normal (CN) older individuals. However, it has been difficult to reliably detect evidence of amyloid-related cognitive alterations in CN using standard neuropsychological measures. We sought to determine whether a highly demanding face-name associative memory exam (FNAME) could detect evidence of A β -related memory impairment in CN. We studied 45 CN subjects (mean age=71.7 \pm 8.8) with Clinical Dementia Rating (CDR) scores=0 and MMSE \geq 28, using Positron Emission Tomography with Pittsburgh Compound B (PiB PET). Memory factor scores were derived from a principal components analysis for FNAME name retrieval (FN-N), FNAME occupation retrieval (FN-O) and the 6-Trial Selective Reminding Test (SRT). Using multiple linear and logistic regression analyses, we related the memory factor scores to PiB distribution volume ratios (DVR, cerebellar reference) as either a continuous or a dichotomous variable in frontal cortex and a posterior cortical region representing the precuneus, posterior cingulate and lateral parietal cortices (PPCLP), co-varying for age and AMNART IQ (a proxy of cognitive reserve (CR)). A significant inverse relationship for FN-N was found with A β deposition in frontal (R(2)=0.29, β =-2.2, p=0.02) and PPCLP cortices (R(2)=0.26, β =-2.4, p=0.05). In contrast, neither FN-O nor the SRT were significantly related to A β deposition. Performance on a demanding test of face-name associative memory was related to A β burden in brain regions associated with memory systems. Associative memory for faces and names, a common complaint among older adults, may be a sensitive marker of early A β -related impairment.

Neurology

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Disruption of limbic white matter pathways in mild cognitive impairment and Alzheimer's disease: A DTI/FDG-PET Study.

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Background: Alzheimer's disease (AD) and mild cognitive impairment (MCI) affect the limbic system, causing medial temporal lobe (MTL) atrophy and posterior cingulate cortex (PCC) hypometabolism. Additionally, diffusion tensor imaging (DTI) studies have demonstrated that MCI and AD involve alterations in cerebral white matter (WM) integrity. Objectives: To test if (1) patients with MCI and AD exhibit decreases in the integrity of limbic WM pathways; (2) disconnection between PCC and MTL, manifested as disruption of the cingulum bundle, contributes to PCC hypometabolism during incipient AD. Methods: We measured fractional anisotropy (FA) and volume of the fornix and cingulum using DTI in 23 individuals with MCI, 21 with mild-to-moderate AD, and 16 normal control (NC) subjects. We also measured PCC metabolism using (18) F-fluorodeoxyglucose positron emission tomography (FDG-PET) in AD and MCI patients. Results: Fornix FA and volume were reduced in MCI and AD to a similar extent. Descending cingulum FA was reduced in AD while volume was reduced in MCI and even more so in AD. Both FA and volume of the fornix and descending cingulum reliably discriminated between NC and AD. Fornix FA and descending cingulum volume also reliably discriminated between NC and MCI. Only descending cingulum volume reliably discriminated between MCI and AD. In the combined MCI-AD cohort, PCC metabolism directly correlated with both FA and volume of the descending cingulum. Conclusions: Disruption of limbic WM pathways is evident during both MCI and AD. Disconnection of the PCC from MTL at the cingulum bundle contributes to PCC hypometabolism during incipient AD

Neurology. 2011 Jun 14;76(24):e1114.

Teaching NeuroImages: primary progressive aphasia: PET demonstration.

Tarlaci S, Savas R, Kocacelebi K.

Source

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Alzheimer Dis Assoc Disord. 2011 Jun 9. [Epub ahead of print]

Greater Responsiveness to Donepezil in Alzheimer Patients With Higher Levels of Acetylcholinesterase Based on Attention Task Scores and a Donepezil PET Study.

Kasuya M, Meguro K, Okamura N, Funaki Y, Ishikawa H, Tanaka N, Iwata R, Yanai K.

Source

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The aim of the study was to predict donepezil responders among patients with Alzheimer disease (AD) based on cognitive tests and positron emission tomography. The Mini-Mental State Examination, Digit Symbol subtest (DigSm) of Wechsler Adult Intelligence Scale Revised, and Trail-Making Test A were administered for 80 patients with AD to assess global function, attention, and executive function, respectively. The same tests and the Clinical Global Impression (CGI) scale were conducted after treatment with oral donepezil (5 mg/d) for 6 months (study 1). [C]-Donepezil positron emission tomography examinations were conducted before and after treatment for 30 randomly selected patients. The distribution volume (DV), which indicates the density of donepezil-binding sites, was calculated using Logan graphical analysis (study 2). In study 1, 35 patients were identified as responders based on the CGI and Mini-Mental State Examination changes. These patients had higher baseline DigSm scores compared with nonresponders. In study 2, 15 patients were responders. DigSm correlated with DV at baseline. DV at baseline and %DV change in responders were higher than in nonresponders, and these variables correlated with Δ DigSm and CGI scores. Higher baseline attention may predict responsiveness to donepezil in patients with AD, and higher acetylcholinesterase levels result in a greater clinical effect.

Neurology

Brain Dev. 2011 Oct;33(9):796-805. Epub 2011 Jun 12.

Epilepsy in succinic semialdehyde dehydrogenase deficiency, a disorder of GABA metabolism.

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Succinic semialdehyde dehydrogenase (SSADH) deficiency is a gamma-aminobutyric acid (GABA) degradative defect. Epilepsy affects half of patients. The murine model is associated with a transition from absence to convulsive seizures in the third week, with fatal status epilepticus. The clinical phenotype is reported from a patient database. Flumazenil-Positron Emission Tomography (FMZ-PET) and Transcranial Magnetic Stimulation (TMS) were used to study GABA neurotransmission. Electroencephalography, single cell electrophysiology, and radioligand binding studies are reported from animal studies. Generalized seizures predominate, including tonic-clonic, atypical absence, and myoclonic. EEG discharges are typically generalized spike-wave. MRI shows a dentatopallidolysian pattern. Sudden Unexpected Death in Epilepsy Patients (SUDEP) has occurred and the associated neuropathology reveals chronic excitotoxic injury in globus pallidus. Investigations using FMZ-PET and TMS support downregulation of GABA(A) and GABA(B) activity, respectively, in patients. Gamma-hydroxybutyrate (GHB) induces spike-wave discharges in homozygous null mice via GHB and GABA(B)-mediated mechanisms. These resemble absence seizures and are abolished by a GABA(B) receptor antagonist. Decreased binding of GABA(A) and GABA(B) receptor antagonists has been demonstrated in P19 and P14 null mice, respectively. Downregulation of GABA(A) and GABA(B) receptor subunits is observed by P14. GABA(A) and GABA(B) mediated potentials are reduced from P8-P14. Generalized epilepsy and epileptiform discharges are characteristic of SSADH deficiency. Spontaneous absence seizures appear in null mice by the third week, which may be induced by GHB or GABA(B) activity. Subsequent overuse dependent downregulation of GABA(A) and GABA(B) receptor activity may be associated with hyperexcitability concomitant with the transition to generalized seizures.

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Abnormal Brain Protein Synthesis in Language Areas of Children With Pervasive Developmental Disorder: A L-[1-11C]-Leucine PET Study.

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This study was performed to evaluate the cerebral protein synthesis rate of language brain regions in children with developmental delay with and without pervasive developmental disorder. The authors performed L-[1-(11)C]-leucine positron emission tomography (PET) on 8 developmental delay children with pervasive developmental disorder (mean age, 76.25 months) and 8 developmental delay children without pervasive developmental disorder (mean age, 77.63 months). They found a higher protein synthesis rate in developmental delay children with pervasive developmental disorder in the left posterior middle temporal region ($P = .014$). There was a significant correlation of the Gilliam Autism Rating Scale autism index score with the protein synthesis rate of the left posterior middle temporal region ($r = .496$, $P = .05$). In addition, significant asymmetric protein synthesis (right > left) was observed in developmental delay children without pervasive developmental disorder in the middle frontal and posterior middle temporal regions ($P = .03$ and $P = .04$, respectively). In conclusion, abnormal language area protein synthesis in developmentally delayed children may be related to pervasive symptoms.

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Postural imbalance and falls in PSP correlate with functional pathology of the thalamus.

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To determine how postural imbalance and falls are related to regional cerebral glucose metabolism (PET) and functional activation of the cerebral postural network (fMRI) in patients with progressive supranuclear palsy (PSP). Sixteen patients with PSP, who had self-monitored their frequency of falls, underwent a standardized clinical assessment, posturographic measurement of balance during modified sensory input, and a

resting [18 F]FDG-PET. In addition, patients performed an fMRI paradigm using mental imagery of standing. Results were compared to healthy

controls ($n = 16$). The frequency of falls/month in patients (range 1-40) correlated with total PSP rating score ($r = 0.90$). Total sway path in PSP significantly correlated with frequency of falls, especially during modulated sensory input (eyes open: $r = 0.62$, eyes closed: $r = 0.67$, eyes open/head extended: $r = 0.84$, eyes open/foam-padded platform: $r = 0.87$). Higher sway path values and frequency of falls were associated with

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decreased regional glucose metabolism (rCGM) in the thalamus (sway path: $r = -0.80$, falls: $r = -0.64$) and increased rCGM in the precentral gyrus (sway path: $r = 0.79$, falls: $r = 0.64$). Mental imagery of standing during fMRI revealed a reduced activation of the mesencephalic brainstem tegmentum and the thalamus in patients with postural imbalance and falls. The new and clinically relevant finding of this study is that imbalance and falls in PSP are closely associated with thalamic dysfunction. Deficits in thalamic postural control get most evident when balance is assessed during modified sensory input. The results are consistent with the hypothesis that reduced thalamic activation via the ascending brainstem projections may cause postural imbalance in PSP.

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Neurosurgical treatment of tuberous sclerosis complex lesions.

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Tuberous sclerosis complex (TSC) is an autosomal dominantly inherited syndrome. Renal disease is the main cause of death. Brain disorders are the origin of more frequent and severe problems, such as tumors, epilepsy, and mental retardation. Participation of neurosurgeons in the study and especially in the treatment of TSC patients is often required. Two types of pathological conditions mainly require neurosurgical interventions in TSC: subependymal giant cell astrocytomas (SGCA) and cortical tubers. SGCA are located in the cerebral region close to the foramina of Monroe, uni- or bilaterally, and originate in hamartomas that can grow slowly as well as rapidly, even suddenly, especially in cases with intratumoral cyst, causing increased intracranial pressure (ICP) with severe risk for visual loss and life. Neurosurgeons have to participate in the follow-up of the patients as soon as the risk of ICP exists to remove the tumor when the criteria of SGCA growth are present. The other intracranial lesions that require neurosurgical intervention by are the cortical tubers. These dysplastic lesions are associated with TSC in almost the 100% of affected persons and are the cause of epilepsy in most patients. The seizures can be resistant to antiepileptic medication in many cases in which a tuber is identified as the origin of the focal seizures after functional studies, such as EEG, MR, PET, etc. In these cases, only surgical removal of the tuber and the perituberal epileptogenic foci can cure the epilepsy. Large tubers are more epileptogenic than smaller ones.

Childs Nerv Syst. 2011 Aug;27(8):1197-202. Epub 2011 May 24.

Fiber tractography assessment in double cortex syndrome.

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Source

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Subcortical band heterotopia (SBH) or double cortex syndrome is a malformation of cortical development that may be related to intractable epilepsy and severe mental retardation or to mild epilepsy and slight mental delay or normal cognitive functions. Several studies have been performed using neuroradiological or neurophysiological techniques, like SPECT, PET, MRS, fMRI, and MEG, in attempt to better characterize this neuronal migration disorder. Recently, also diffusion tensor imaging (DTI) and fiber tracking (FT) have been used to investigate on white matter anomalies in SBH, adding more information about such gray matter anomaly. We report on three cases of SBH, evaluated with MRI, DTI, and FT. The data gathered from DTI and TF allow us to hypothesize a new functional role for heterotopia

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Adenosine 2A receptor availability in dyskinetic and nondyskinetic patients with Parkinson disease.

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To investigate striatal adenosine A2A receptor availability in patients with Parkinson disease (PD) with and without levodopa-induced dyskinesias (LIDs). While providing effective relief from the motor symptoms of PD, chronic levodopa use is associated with development of LIDs. A2A receptors are expressed on the bodies of indirect pathway medium spiny striatal neurons and on dopamine terminals and play a role in modulating dopamine transmission. A2A antagonists have antiparkinsonian activity by boosting levodopa efficacy. We aimed to study A2A receptor availability in patients with PD with and without LIDs using PET and [¹¹C]SCH442416, an A2A antagonist. Six patients with PD with and 6 without LIDs were studied withdrawn 12 hours from medication. Their PET findings were compared with 6 age-matched healthy controls. Using spectral analysis, [¹¹C]SCH442416 regional volumes of distribution (V(T)) were computed for the caudate, putamen, and thalamus and binding potentials (BP(ND)) reflecting the ratio of specific:non-specific uptake were compared between groups. A2A binding in the caudate and putamen of subjects with PD with LIDs was far higher ($p = 0.026$ and $p = 0.036$, respectively) than that of subjects with PD without LIDs, which

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lay within the control range. Thalamic A2A availability was similar for all 3 groups. Patients with PD with LIDs show increased A2A receptor availability in the striatum. This finding is compatible with altered adenosine transmission playing a role in LIDs and provides a rationale for a trial of A2A receptor agents in the treatment of these motor complications.

Neurobiol Dis. 2011 Sep;43(3):565-75. Epub 2011 May 13.

[F-18]FDDNP microPET imaging correlates with brain A β burden in a transgenic rat model of Alzheimer disease: effects of aging, in vivo blockade, and anti-A β antibody treatment.

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In vivo detection of Alzheimer's disease (AD) neuropathology in living patients using positron emission tomography (PET) in conjunction with high affinity molecular imaging probes for β -amyloid (A β) and tau has the potential to assist with early diagnosis, evaluation of disease progression, and assessment of therapeutic interventions. Animal models of AD are valuable for exploring the in vivo binding of these probes, particularly their selectivity for specific neuropathologies, but prior PET experiments in transgenic mice have yielded conflicting results. In this work, we utilized microPET imaging in a transgenic rat model of brain A β deposition to assess [F-18]FDDNP binding profiles in relation to age-associated accumulation of neuropathology. Cross-sectional and longitudinal imaging demonstrated that [F-18]FDDNP binding in the hippocampus and frontal cortex progressively increases from 9 to 18 months of age and parallels age-associated A β accumulation. Specificity of in vivo [F-18]FDDNP binding was assessed by naproxen pretreatment, which reversibly blocked [F-18]FDDNP binding to A β aggregates. Both [F-18]FDDNP microPET imaging and neuropathological analyses revealed decreased A β burden after intracranial anti-A β antibody administration. The combination of this non-invasive imaging method and robust animal model of brain A β accumulation allows for future longitudinal in vivo assessments of potential therapeutics for AD that target A β production, aggregation, and/or clearance. These results corroborate previous analyses of [F-18]FDDNP PET imaging in clinical populations.

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In vivo functional brain imaging and a therapeutic trial of l-arginine in MELAS patients.

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Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is the most common type of mitochondrial disease and is characterized by stroke-like episodes (SEs), myopathy, lactic acidosis, diabetes mellitus, hearing-loss and cardiomyopathy. The causal hypotheses for SEs in MELAS presented to date are angiopathy, cytopathy and neuronal hyperexcitability. l-arginine (Arg) has been applied for the therapy in MELAS patients. Recent advanced in vivo imaging techniques such as MRI, MRS and PET were applied for evaluating the pathogenesis of SEs (i.e. angiopathy and cytopathy) and monitoring the biochemical effects of l-Arg. Administration of l-Arg to MELAS patients has been successful in reducing neurological symptoms due to acute strokes and preventing recurrences of SEs in the chronic phase. l-Arg has dual pharmaceutical effects on both angiopathy and cytopathy in MELAS. In vivo functional brain imaging promotes a better understanding of the pathogenesis and potential therapies for MELAS patients.

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Novel FDG-PET Findings in Anti-NMDA Receptor Encephalitis: A Case Based Report.

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The clinical manifestation and nuclear imaging findings in a 15-year-old boy with anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis are described in this case report. The previously healthy patient presented with new onset hallucinations, seizure, and within a week, his mental status rapidly deteriorated to nonverbal with oro-lingual-facial dyskinesias. An extensive laboratory work-up for encephalopathy was negative. Repeated brain magnetic resonance imaging (MRI) studies were normal. On day 26 of admission, nuclear imaging using fluorodeoxyglucose positron emission tomography (FDG-PET) showed global hypometabolism with a prominent focally intense hypermetabolic lesion in the right cerebellar cortex. Diagnosis of anti-NMDAR encephalitis was confirmed with quantitative serology. The patient showed clinical signs of improvement after 2 courses of intravenous immunoglobulin therapy over 4 weeks. On day 46, repeat brain FDG-PET showed overall improvement but in contrast to the previous, the right cerebellar cortex showed focal hypometabolism. This is the first reported case of such findings using FDG-PET in anti-NMDAR encephalitis.

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Partial exchange transfusion results in increased cerebral oxygenation and faster peripheral microcirculation in newborns with polycythemia.

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Aim: The aim of this study was to assess cerebral and peripheral oxygenation, by using near infrared spectroscopy (NIRS) and microcirculation by using side stream dark field (SDF) imaging in newborns with polycythemia before and after partial exchange transfusion (PET) therapy to investigate treatment effect on tissue oxygenation and microcirculation. **Methods:** Polycythemic newborns with venous haematocrit (Htc) >70% or ≥65% with symptoms were included. NIRS measurements for cerebral and peripheral oxygenation and SDF recordings for microcirculatory flow assessment were obtained before and after PET. Fractional tissue oxygen extraction (FTOE) was calculated based on tissue oxygenation index and oxygen saturation. Wilcoxon test was used for statistical analysis. **Results:** Fifteen newborns were included. Cerebral tissue oxygenation index, microvascular flow index and % of vessels with hyperdynamic flow increased after PET; median (range): 61.27 (51.36-61.87) versus 64.54 (54.1-74.38), 2.74 (2.46-3) versus 3.22 (2.64-3.75) and 0 (0-2.8) versus 3 (0-99.3), respectively. Whereas cerebral fractional tissue oxygen extraction (cFTOE), % of vessels with sluggish flow decreased after treatment; 0.36 (0.22-0.44) versus 0.31 (0.17-0.46), 1.4 (0-69) versus 0 (0-0.9), respectively. Peripheral oxygenation was unchanged. **Conclusion:** Partial exchange transfusion improves microcirculation in polycythemic newborns. Cerebral oxygenation increases and cFTOE decreases suggesting increased blood flow. Microvascular flow increases possibly representing reactive hyperperfusion after hemodilution. Whether these effects are beneficial require further research.

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Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B.

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Subcortical vascular dementia (SVaD) is considered the most common type of vascular dementia and often follows a slowly progressive course, simulating Alzheimer disease (AD). Whether the progressive cognitive decline is associated with pure SVaD or concomitant AD remains unknown. The purpose of this study was to determine what proportion of patients with SVaD lack abnormal amyloid imaging, and to examine differences in the clinical or MRI features between subjects with SVaD with cortical amyloid deposition and those without. We measured brain amyloid deposition using (11)C-Pittsburgh compound B (PiB) PET in 45 patients (men: women = 19:26; mean age 74.2 ± 7.6 years) with SVaD. They all met DSM-IV criteria for vascular dementia and had severe white matter high signal intensities without territorial infarction or macrohemorrhage on MRI. Thirty-one (68.9%) of 45 patients with SVaD were negative for cortical PiB binding. There was significant difference between (11)C-PiB-positive and (11)C-PiB-negative groups in terms of age (79.5 vs 71.9 years), Mini-Mental State Examination score (18.6 vs 22.6), the number of lacunes (3.9 vs 9.0), and the visual rating scale of hippocampal atrophy (3.1 vs 2.3). The neuropsychological assessments revealed that patients with (11)C-PiB-negative SVaD performed better on the delayed recall of both the verbal and visual memory test than did those with (11)C-PiB-positive scan. SVaD without abnormal amyloid imaging was more common than expected. Patients with SVaD with and without abnormal amyloid imaging differed in clinical and MRI features, although there was

Epilepsia. 2011 Sep;52(9):1692-8. doi: 10.1111/j.1528-1167.2011.03103.x. Epub 2011 May 13.

Clinical and histopathologic correlates of (11) C-alpha-methyl-l-tryptophan (AMT) PET abnormalities in children with intractable epilepsy.

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Purpose: Interictal increase of (11) C-alpha-methyl-l-tryptophan (AMT) on positron emission tomography (PET) can be seen in cortical epileptic foci, and is particularly common in cortical developmental malformations. Therefore, in the present study, we evaluated the clinical and histopathologic correlates of AMT-PET abnormalities in children with intractable epilepsy undergoing resective surgery. **Methods:** Thirty children (mean age: 6.7 ± 3.2 years) were included in this study. All patients received AMT-PET as part of their presurgical evaluation and subsequently underwent epilepsy surgery. Magnetic resonance imaging (MRI) scans were normal in 15, showed nonspecific changes in 8, and suggested malformations of cortical development (MCDs) in nine children. Asymmetry indices (AIs) were calculated to determine increased AMT uptake. **Key Findings:** Histopathology revealed MCDs in 16 (53%) children, including 12 with cortical dysplasia (CD) [mild MCD = 3; CD type IA = 2; CD type IIA = 2 and CD type IIB (severe CD with balloon cells) = 5]. Polymicrogyria and heterotopias (P&Hs) were seen in three cases and subependymal heterotopias (SEHs) in one child. The remaining 14 cases showed normal histopathology with

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varying degrees of gliosis. Increased AMT uptake was found in all five with CD type IIB, and all three with P&H, but in none with mild MCD and types IA-IIA CD or SEH. Whereas all five children with CD IIB and two with P&H had excellent surgical outcome (class I); children with milder CD or SEH had variable surgical outcome. The 14 patients with normal histopathology included seven patients with focally increased and seven with normal AMT uptake. Although patients with normal pathology and normal AMT-PET had better surgical outcome (class I = 5; II = 2), those with normal pathology, normal MRI, but abnormal AMT-PET had poor surgical outcome (class III = 4; IV = 3). Significance: Increased AMT uptake in children with CD may predict type IIB dysplasia (with balloon cells) and good surgical outcome. Histopathologic similarities between CD type IIB and epileptogenic cortical tubers may imply a common role of the inflammatory kynurenine pathway of tryptophan metabolism in these lesions. In children with normal histopathology, there is a subgroup with increased AMT uptake and poor surgical outcome.

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Regional grey matter loss and brain disconnection across Alzheimer disease evolution.

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It is becoming increasingly clearer that the clinical manifestations of Alzheimer's disease (AD) are not only associated with regional grey matter (GM) damage, but also with abnormal integration between cortical brain regions by disconnection mechanism. This concept comes from the evidence that white matter (WM) damage (as assessed by diffusion MR imaging) can be observed in patients with AD since the early clinical stages, and it correlates with clinical measures of cognitive disability. In this perspective, several functional imaging studies, based on PET and resting state fMRI, have provided evidence that brain hypometabolism/disconnection may precede the occurrence of GM atrophy in certain regions of AD brains, such as the cingulate cortex. The cingulum represents the most prominent WM tract of the limbic system, being directly connected to the medial temporal lobe structures. Therefore, this structure likely contributes to changes in functional connectivity observed within the so called default-mode network of AD patients, and its damage is likely to play a remarkable role in the conversion from mild cognitive impairment (MCI) to dementia. Nowadays, the combination of several neuroimaging techniques that provide both, measures of regional GM loss and measures of functional and structural connectivity offer the opportunity to investigate in vivo the pathophysiological changes of brain tissue modifications across the clinical evolution of AD. This paper reviews the main MR based methods of investigation of brain tissue involvement in patients with AD and MCI, and the role they have played in clarifying the differential contribution of GM damage and brain disconnection to AD pathophysiology. This subject seems to be relevant for both, speculative aspects of neurology and application to clinical trials.

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Reversible abnormal functional neuroimaging presentations in polycythemia vera with chorea.

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We report a case of polycythemia vera with chorea in which the brain metabolism and dopamine system were investigated using 2-[(18)F]fluoro-2-deoxy-D: -glucose positron emission tomography (FDG PET) and (99m)Tc-labeled tropane dopamine transporter ((99m)Tc-TRODAT-1) single photon emission computed tomography (SPECT). Along with normalization of the hematocrit and clinical symptoms after consecutive phlebotomies, the FDG PET scan and (99m)Tc-TRODAT-1 SPECT images returned towards normal. It is hypothesized that the development of polycythemia chorea is associated with a reversible alteration in the corticobasal ganglia metabolism and disturbed dopaminergic function.

J Cereb Blood Flow Metab. 2011 May 11. [Epub ahead of print]

Bilateral transcranial direct current stimulation modulates activation-induced regional blood flow changes during voluntary movement.

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Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that induces changes in cortical excitability: anodal stimulation increases while cathodal stimulation reduces excitability. Imaging studies performed after unilateral stimulation have shown conflicting results regarding the effects of tDCS on surrogate markers of neuronal activity. The aim of this study was to directly measure these effects on activation-induced changes in regional cerebral blood flow (Δ rCBF) using positron emission tomography (PET) during bilateral tDCS. Nine healthy subjects underwent repeated rCBF measurements with (15)O-water and PET during a simple motor task while receiving tDCS or sham stimulation over the primary motor cortex (M1). Motor evoked potentials (MEPs) were also assessed before and after real and sham

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stimulation. During tDCS with active movement, Δ rCBF in M1 was significantly lower on the cathodal than the anodal side when compared with sham stimulation. This decrease in Δ rCBF was accompanied by a decrease in MEP amplitude on the cathodal side. No effect was observed on resting or activated rCBF relative to sham stimulation. We thus conclude that it is the interaction of cathodal tDCS with activation-induced Δ rCBF rather than the effect on resting or activated rCBF itself which constitutes the physiological imaging correlate of tDCS

Brain Imaging Behav. 2011 Sep;5(3):203-11. doi: 10.1007/s11682-011-9124-5.

A longitudinal study of motor performance and striatal [18F]fluorodopa uptake in Parkinson's disease.

Gallagher CL, Johnson SC, Bendlin BB, Chung MK, Holden JE, Oakes TR, Brooks BR, Konopacki RA, Dogan S, Abbs JH, Xu G, Nickles RJ, Pyszalski RW, DeJesus OT, Brown WD.

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Although [(18)F]fluoro-L: -dopa [FDOPA] positron emission tomography (PET) has been used as a surrogate outcome measure in Parkinson's disease therapeutic trials, this biomarker has not been proven to reflect clinical status longitudinally. We completed a retrospective analysis of relationships between computerized sampling of motor performance, FDOPA PET, and clinical outcome scales, repeated over 4 years, in 26 Parkinson's disease (PD) patients and 11 healthy controls. Mixed effects analyses showed that movement time and tongue strength best differentiated PD from control subjects. In the treated PD cohort, motor performance measures changed gradually in contrast to a steady decline in striatal FDOPA uptake. Prolonged reaction and movement time were related to lower caudate nucleus FDOPA uptake, and abnormalities in hand fine force control were related to mean striatal FDOPA uptake. These findings provide evidence that regional loss of nigrostriatal inputs to frontostriatal networks affects specific aspects of motor function.

Neurology. 2011 May 10;76(19):1623-30.

A family with Parkinsonism, essential tremor, restless legs syndrome, and depression.

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Previous epidemiologic and genetic studies have suggested a link between Parkinson disease (PD), essential tremor (ET), and restless legs syndrome (RLS). We describe the clinical, PET, and pathologic characteristics of an extensive kindred from Arkansas with hereditary PD, ET, and RLS. The pedigree contains 138 individuals. Sixty-five family members were examined neurologically up to 3 times from 2004 to 2010. Clinical data were collected from medical records and questionnaires. Genetic studies were performed. Five family members underwent multitracer PET. Two individuals with PD were examined postmortem. Eleven family members had PD with generally mild and slowly progressive symptoms. Age at onset was between 39 and 74 years (mean 59.1, SD 13.4). All individuals treated with l-dopa responded positively. Postural or action tremor was present in 6 individuals with PD, and in 19 additional family members. Fifteen persons reported symptoms of RLS. PET showed reduced presynaptic dopamine function typical of sporadic PD in a patient with PD and ET, but not in persons with ET or RLS. The inheritance pattern was autosomal dominant for PD and RLS. No known pathogenic mutation in PD-related genes was found. Fourteen of the family members with PD, ET, or RLS had depression. Neuropathologic examination revealed pallidonigral pigment spheroid degeneration with ubiquitin-positive axonal spheroids, TDP43-positive pathology in the basal ganglia, hippocampus, and brainstem, and only sparse Lewy bodies. Familial forms of PD, ET, RLS, and depression occur in this family. The genetic cause remains to be elucidated.

Eur J Neurol. 2011 May 7. doi: 10.1111/j.1468-1331.2011.03423.x. [Epub ahead of print]

Psychogenic amnesia and self-identity: a multimodal functional investigation.

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Department of Neurology, Hadassah Hebrew University Medical Center, Jerusalem, Israel Department of Neurology, University Hospital, Geneva Laboratory of Cognitive Neuroscience, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne Department of Nuclear Medicine, University Hospital, Geneva Department of Radiology, University Hospital, Geneva, Switzerland Department of Neurology, Johns Hopkins Bayview Medical Center, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Background: Patients with psychogenic amnesia generally suffer from episodic memory deficits associated with an impairment of self-identity. While the first is generally attributed to limbic dysfunction, the latter might be related to posterior parietal cortex. Methods and Results: In a patient with acute repetitive psychogenic amnesia, three different functional investigations (fMRI, electrical-neuroimaging, PET) during both resting-state and a behavioural paradigm testing 'time-travel' showed left posterior parietal activation, unlike in 12 control subjects. Conclusion: Impairment of self-identity and episodic memory in psychogenic amnesia may be associated with functional alterations of left posterior parietal cortex.

Neurology

Int J Alzheimers Dis. 2011 Apr 10;2011:280289.

Magnetoencephalography as a putative biomarker for Alzheimer's disease.

Zamrini E, Maestu F, Pekkonen E, Funke M, Makela J, Riley M, Bajo R, Sudre G, Fernandez A, Castellanos N, Del Pozo F, Stam CJ, van Dijk BW, Bagic A, Becker JT.

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Alzheimer's Disease (AD) is the most common dementia in the elderly and is estimated to affect tens of millions of people worldwide. AD is believed to have a prodromal stage lasting ten or more years. While amyloid deposits, tau filaments, and loss of brain cells are characteristics of the disease, the loss of dendritic spines and of synapses predate such changes. Popular preclinical detection strategies mainly involve cerebrospinal fluid biomarkers, magnetic resonance imaging, metabolic PET scans, and amyloid imaging. One strategy missing from this list involves neurophysiological measures, which might be more sensitive to detect alterations in brain function. The Magnetoencephalography International Consortium of Alzheimer's Disease arose out of the need to advance the use of Magnetoencephalography (MEG), as a tool in AD and pre-AD research. This paper presents a framework for using MEG in dementia research, and for short-term research priorities.

Psychiatry Res. 2011 Jun 30;192(3):183-7. Epub 2011 May 4.

Improved social interaction and increased anterior cingulate metabolism after group reminiscence with reality orientation approach for vascular dementia.

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A group reminiscence approach (GRA) with reality orientation (RO) is widely used as a psychosocial intervention for dementia. Since clinical effectiveness was reported for the intervention, interest has been directed toward areas of the neuronal network that might be being stimulated. We hypothesized that the frontal lobe associated with social interaction was being stimulated. To test this hypothesis, we studied 24 patients with vascular dementia. In addition to conventional care, a 1-h session of GRA with RO was provided once a week for 3 months in the GRA-RO arm (n=12). Only supportive care was provided in the control arm (n=12). Before and after the interventions, cognitive function, depressive state, and social activities were assessed. Since glucose metabolism is associated with brain function, cerebral glucose metabolism was measured by positron emission tomography (PET). Regarding behavioral improvement, 10 patients in the GRA-RO arm showed improvement compared with only two patients in the control arm, a significant difference. PET demonstrated that metabolism in the anterior cingulate was increased in the GRA-RO arm, whereas no significant changes were observed in the control arm. These results suggest that GRA-RO stimulates the anterior cingulate and has a positive effect on social interaction.

Neurology. 2011 May 24;76(21):1789-96. Epub 2011 Apr 27.

Distinct clinical and metabolic deficits in PCA and AD are not related to amyloid distribution.

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Patients with posterior cortical atrophy (PCA) often have Alzheimer disease (AD) at autopsy, yet are cognitively and anatomically distinct from patients with clinical AD. We sought to compare the distribution of β -amyloid and glucose metabolism in PCA and AD in vivo using Pittsburgh compound B (PiB) and FDG-PET. Patients with PCA (n = 12, age 57.5 ± 7.4 , Mini-Mental State Examination [MMSE] 22.2 ± 5.1), AD (n = 14, age 58.8 ± 9.6 , MMSE 23.8 ± 6.7), and cognitively normal controls (NC, n = 30, age 73.6 ± 6.4) underwent PiB and FDG-PET. Group differences in PiB distribution volume ratios (DVR, cerebellar reference) and FDG uptake (pons-averaged) were assessed on a voxel-wise basis and by comparing binding in regions of interest (ROIs). Compared to NC, both patients with AD and patients with PCA showed diffuse PiB uptake throughout frontal, temporoparietal, and occipital cortex ($p < 0.0001$). There were no regional differences in PiB binding between PCA and AD even after correcting for atrophy. FDG patterns in PCA and AD were distinct: while both groups showed hypometabolism compared to NC in temporoparietal cortex and precuneus/posterior cingulate, patients with PCA further showed hypometabolism in inferior occipitotemporal cortex compared to both NC and patients with AD ($p < 0.05$). Patients with AD did not show areas of relative hypometabolism compared to PCA. Fibrillar amyloid deposition in PCA is diffuse and similar to AD, while glucose hypometabolism extends more posteriorly into occipital cortex. Further studies are needed to determine the mechanisms of selective network degeneration in focal variants of AD.

Neurology

Headache. 2011 May;51(5):752-78. doi: 10.1111/j.1526-4610.2011.01892.x.

One hundred years of migraine research: major clinical and scientific observations from 1910 to 2010.

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Pain research, and headache research in particular, during the 20th century, has generated an enormous volume of literature promulgating theories, questions, and temporary answers. This narrative review describes the most important events in the history of migraine research between 1910 and 2010. Based on the standard textbooks of headache: Wolff's Headache (1948 and 1963) and The Headaches (1993, 2000, and 2006) topics were selected for a historical review. Most notably these included: isolation and clinical introduction of ergotamine (1918); further establishment of vasodilation in migraine and the constrictive action of ergotamine (1938); identification of pain-sensitive structures in the head (1941); Lashley's description of spreading scotoma (1941); cortical spreading depression (CSD) of Leão (1944); serotonin and the introduction of methysergide (1959); spreading oligemia in migraine with aura (1981); oligemia in the wake of CSD in rats (1982); neurogenic inflammation theory of migraine (1987); a new headache classification (1988); the discovery of sumatriptan (1988); migraine and calcitonin gene-related peptide (1990); the brainstem "migraine generator" and PET studies (1995); migraine as a channelopathy, including research from the genetic perspective (1996); and finally, meningeal sensitization, central sensitization, and allodynia (1996). Pathophysiological ideas have evolved within a limited number of paradigms, notably the vascular, neurogenic, neurotransmitter, and genetic/molecular biological paradigm. The application of various new technologies played an important role within these paradigms, in particular neurosurgical techniques, EEG, methods to measure cerebral blood flow, PET imaging, clinical epidemiological, genetic, and molecular biological methods, the latter putting migraine (at least hemiplegic migraine) within a completely new classification of diseases.

Stroke. 2011 Jun;42(6):1563-8. Epub 2011 Apr 21.

Vessel wall inflammation in spontaneous cervical artery dissection: a prospective, observational positron emission tomography, computed tomography, and magnetic resonance imaging study.

Pfefferkorn T, Saam T, Rominger A, Habs M, Gerdes LA, Schmidt C, Cyran C, Straube A, Linn J, Nikolaou K, Bartenstein P, Reiser M, Hacker M, Dichgans M.

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Vessel wall inflammation (VWI) may be a pathogenetic factor in cervical artery dissection (CAD). We used contrast-enhanced high-resolution MRI (hrMRI) and positron emission tomography CT (PET-CT) to systematically investigate VWI in spontaneous CAD. In this monocentric, prospective, observational study, all consecutive patients with acute, MRI-confirmed, spontaneous CAD admitted to our center between August 2007 and August 2009 were included. VWI was defined as perivascular contrast enhancement in hrMRI and increased perivascular [¹⁸F]-fluorodesoxyglucose uptake in PET-CT. VWI was further differentiated between local (restricted to the site of dissection) and generalized (exceeding the site of dissection). A total of 37 patients were included. Multiple dissections were seen in 10 patients (27%). Twenty-five patients received both modalities as planned, 8 received only PET-CT, and 4 received only hrMRI. A subset of patients showed signs of a generalized VWI in hrMRI (4/29 patients, 14%) and PET-CT (8/33 patients, 24%). In patients who received both modalities, all with hrMRI signs of generalized VWI were PET-CT positive (3/3), whereas some PET-CT-positive patients were hrMRI-negative (4/7). If present, generalized VWI in hrMRI completely resolved within 6 months. The presence of >2 simultaneous dissections (seen in 2 patients) was significantly associated with generalized VWI in hrMRI (P=0.015) but marginally not in PET-CT (P=0.053). A subset of patients with spontaneous CAD showed signs of a generalized transient inflammatory arteriopathy in contrast-enhanced hrMRI and PET-CT. This subset of patients may be more prone to multiple dissections.

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FDG-PET and MRI features in multiple system atrophy.

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Neurology

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Role of single photon emission computed tomography in epilepsy.

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Molecular imaging with ictal single photon emission computed tomography (SPECT) is an established functional imaging modality for the presurgical evaluation of patients with refractory partial onset seizures. SPECT coregistered on to the MRI has greater sensitivity to identify the ictal onset zone. Ictal SPECT should always be interpreted in the context of other presurgical investigations. Ictal SPECT is sensitive method for the lateralization of TLE, but ictal SPECT is more sensitive when MRI is normal. Ictal SPECT and interictal PET are complementary to each other in lateralizing the side in patients with TLE and normal MRI. In extratemporal epilepsy, ictal SPECT will guide the placement of surface grid and depth electrodes.

Inflamm Res. 2011 Aug;60(8):769-74. Epub 2011 Apr 13.

Soluble vascular endothelial growth factor (VEGF) receptor-1 inhibits migration of human monocytic THP-1 cells in response to VEGF.

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We aimed to investigate the regulation and contribution of vascular endothelial growth factor (VEGF) and sFlt-1(1-3) to human monocytic THP-1 migration.

Ad-sFlt-1/FLAG, a recombinant adenovirus carrying the human sFlt-1(1-3) (the first three extracellular domains of FLT-1, the hVEGF receptor-1) gene, was constructed. L929 cells were infected with Ad-sFlt-1/FLAG and the expression of sFlt-1 was detected by immunofluorescent assay and ELISA. Corning® Transwell® Filter Inserts containing polyethylene terephthalate (PET) membranes with pore sizes of 3 µm were used as an experimental model to simulate THP-1 migration. Five VEGF concentrations (0, 0.1, 1, 10 and 100 ng/ml), four concentrations of sFlt-1(1-3)/FLAG expression supernatants (0.1, 1, 10 and 100 ng/ml), and monocyte chemoattractant protein-1 (MCP-1, 10 ng/ml) were used to test the ability of THP-1 cells to migrate through PET membranes. The sFlt-1(1-3) gene was successfully recombined into Ad-sFlt-1/FLAG. sFlt-1(1-3) was expressed in L929 cells transfected with Ad-sFlt-1/FLAG. THP-1 cell migration increased with increasing concentrations of VEGF, while cell migration decreased with increasing concentrations of sFlt-1(1-3)/FLAG. sFlt-1(1-3)/FLAG had no effect on MCP-1-induced cell migration. This study demonstrated that VEGF is able to elicit a migratory response in THP-1 cells, and that sFlt-1(1-3) is an effective inhibitor of THP-1 migration towards VEGF.

J Neurol. 2011 Apr 10. [Epub ahead of print]

In vivo demonstration of amyloid burden in posterior cortical atrophy: a case series with PET and CSF findings.

Formaglio M, Costes N, Seguin J, Tholance Y, Le Bars D, Rouillet-Solignac I, Mercier B, Krolak-Salmon P, Vighetto A.

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Our objective was to evaluate amyloid deposition in posterior cortical atrophy (PCA), using both cerebrospinal fluid (CSF) biomarker analysis and amyloid imaging. Five PCA patients, selected based on their neuropsychological profile and atrophic changes in posterior regions on MRI, underwent CSF analysis. CSF amyloid-beta 1-42, total tau, and phosphorylated tau at threonine 181 levels were determined. They also had positron emission tomography (PET) with Pittsburgh Compound B ([¹¹C]PIB). [¹¹C]PIB ratio images were assessed with visual, regional and voxel-based analyses and compared to eight typical Alzheimer's disease (AD) patients and eight controls. The biological profile in the five PCA patients, resulting from CSF and [¹¹C]PIB images analysis, was consistent with AD. Individual comparisons of PCA patients' [¹¹C]PIB images with the AD group with Statistical Parametric Mapping (SPM) revealed a distinctive posterior uptake in four out of the five patients showing increased amyloid deposition in occipital, temporal, and/or parietal regions. ROI group analysis showed a tendency for higher amyloid deposition in occipital and temporal regions. However, this pattern was not found with SPM group analysis when the global level of [¹¹C]PIB uptake was used as a covariate. Our results indicate that amyloid burden can be demonstrated in vivo in PCA suggesting a diagnosis of AD. PCA patients may present a higher global amyloid load than AD that was not related to age at onset, disease severity, disease duration, or educational level in our study. Combined CSF and PET biomarkers seem helpful for in vivo diagnosis of this focal syndrome with underlying AD pathology.

Neurology

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11C-PiB PET does not detect PrP-amyloid in prion disease patients including variant Creutzfeldt-Jakob disease.

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J Alzheimers Dis. 2011;25(3):517-23.

Spatial distribution of glucose hypometabolism induced by intracerebroventricular streptozotocin in monkeys.

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Intracerebroventricular injection of streptozotocin (icv-STZ) in rodents induces cellular and behavioral features mimicking Alzheimer's disease (AD). However, the effect of icv-STZ in terms of regional cerebral glucose metabolism has not yet been examined in vivo. Given that regionally specific hypometabolism of glucose is a consistent neuroimaging marker in early AD, we monitored 18F-deoxyglucose uptake using a high-resolution micro-PET after icv-STZ in non-human primates. Two cynomolgus monkeys (*Macaca fascicularis*) received STZ (2 mg/kg), and another two were given normal saline as controls, at the cerebellomedullary cistern (CM) three times (day 1, 7, and 14). FDG-PET, as well as MRI for structural evaluation, was performed immediately before, six weeks after, and 12 weeks after the first icv injection. In the STZ group, FDG uptake decreased significantly in comparison to the pre-injection baseline, at the precuneus, the posterior cingulate, and medial temporal cortices. Increase in sulcal markings suggesting brain atrophy was observed by MRI at six weeks post-injection. The structural changes normalized at 12 weeks, but the reduced FDG uptake persisted at the same loci. The cortical distribution of glucose hypometabolism was similar to that at early stages of AD patients. The findings demonstrate that the effect of icv-STZ is regionally specific, lending further support for the method as a model of AD pathogenesis.

Neurology. 2011 Apr 12;76(15):1296-301. Epub 2011 Apr 6.

Reduced uptake of [¹⁸F]FDOPA PET in asymptomatic welders with occupational manganese exposure.

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Welding exposes workers to manganese (Mn) fumes, but it is unclear if this exposure damages dopaminergic neurons in the basal ganglia and predisposes individuals to develop parkinsonism. PET imaging with 6-[(18)F]fluoro-L-dopa (FDOPA) is a noninvasive measure of nigrostriatal dopaminergic neuron integrity. The purpose of this study is to determine whether welding exposure is associated with damage to nigrostriatal neurons in asymptomatic workers.

We imaged 20 asymptomatic welders exposed to Mn fumes, 20 subjects with idiopathic Parkinson disease (IPD), and 20 normal controls using FDOPA PET. All subjects were examined by a movement disorders specialist. Basal ganglia volumes of interest were identified for each subject. The specific uptake of FDOPA, K(i), was generated for each region using graphical analysis method. Repeated measures general linear model (GLM) analysis demonstrated a strong interaction between diagnostic group and region ($F(4,112) = 15.36, p < 0.001$). Caudate K(i)s were lower in asymptomatic welders (0.0098 ± 0.0013 minutes⁻¹) compared to control subjects (0.0111 ± 0.0012 minutes⁻¹), $p = 0.002$. The regional pattern of uptake in welders was most affected in the caudate > anterior putamen > posterior putamen. This uptake pattern was anatomically reversed from the pattern found in subjects with IPD. Active, asymptomatic welders with Mn exposure demonstrate reduced FDOPA PET uptake indicating dysfunction in the nigrostriatal dopamine system. The caudate K(i) reduction in welders may represent an early (asymptomatic) marker of Mn neurotoxicity and appears to be distinct from the pattern of dysfunction found in symptomatic IPD.

Neurology

Clin Nucl Med. 2011 May;36(5):394-6.

Focal cerebral hypermetabolism due to nonconvulsive status epilepticus mimicking metastasis in staging a patient with lung cancer by FDG PET/CT.

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J Psychiatry Neurosci. 2011 Mar 1;36(2):100117. doi: 10.1503/jpn.100117. [Epub ahead of print]

Monoamine oxidase A inhibitor occupancy during treatment of major depressive episodes with moclobemide or St. John's wort: an [(11)C]-harmine PET study.

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Background: Monoamine oxidase A (MAO-A) inhibitor antidepressants raise levels of multiple monoamines, whereas the selective serotonin reuptake inhibitors (SSRIs) only raise extracellular serotonin. Despite this advantage of MAO-A inhibitors, there is much less frequent development of MAO inhibitors compared with SSRIs. We sought to measure brain MAO-A occupancy after 6 weeks of treatment in depressed patients with a clinically effective dose of a selective MAO-A inhibitor and measure MAO-A occupancy after repeated administration of St. John's wort, an herb purported to have MAO-A inhibitor properties. Methods: Participants underwent 2 [(11)C]-harmine positron emission tomography scans. Healthy controls completed a test-retest condition, and depressed patients were scanned before and after repeated administration of moclobemide or St. John's wort for 6 weeks at the assigned dose. We measured MAO-A VT, an index of MAO-A density, in the prefrontal, anterior cingulate and anterior temporal cortices, putamen, thalamus, midbrain and hippocampus. Results: We included 23 participants (10 controls and 13 patients with major depressive disorder [MDD]) in our study. Monoamine oxidase A VT decreased significantly throughout all regions after moclobemide treatment in patients with MDD compared with controls (repeated-measures analysis of variance, $F(1,15) = 71.08-130.06$, $p < 0.001$ for all regions, mean occupancy 74% [standard deviation 6%]). Treatment with St. John's wort did not significantly alter MAO-A VT. Limitations: The occupancy estimates are limited by the sample size of each treatment group; hence, our estimate for the overall moclobemide occupancy of 74% has a 95% confidence interval of 70%-78%, and we can estimate with 95% certainty that the occupancy of St. John's wort is less than 5%. Conclusion: For new MAO-A inhibitors, about 74% occupancy at steady-state dosing is desirable. Consistent with this, St. John's wort should not be classified as an MAO-A inhibitor. The magnitude of MAO-A blockade during moclobemide treatment exceeds the elevation of MAO-A binding during illness by at least 30%, suggesting that the treatment effect should exceed the disease effect when designing selective antidepressants for this target.

Pharmacogenomics. 2011 Mar;12(3):379-95.

Central neurotoxicity in cancer chemotherapy: pharmacogenetic insights.

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Central neurotoxicity of chemotherapy is likely to be multifactorial. There are two hypotheses regarding endogenous mechanisms that may be involved, namely the target and the blood-brain barrier transporter hypotheses. Here, we will review candidate genetic determinants for the risk of chemotherapy-induced neurotoxicity, such as polymorphisms involved in the target mechanism. These include polymorphisms in folate metabolizing enzymes and apolipoprotein E, as well as those in blood-brain barrier transporter genes. Currently, the exact role of pharmacogenetics in mechanisms that lead to central neurotoxicity of chemotherapy has not been fully unraveled. Larger, prospective, longitudinal and more uniform studies are needed, with prechemotherapy and follow-up measurements of neuropsychological performance, MRI, PET, genetic profiles and biomarkers relevant for the proposed target and transporter mechanisms.

Mov Disord. 2011 Mar;26(4):614-20. doi: 10.1002/mds.23503. Epub 2011 Mar 29.

Rate of 6-[18F]fluorodopa uptake decline in striatal subregions in Parkinson's disease.

Gallagher CL, Oakes TR, Johnson SC, Chung MK, Holden JE, Bendlin BB, McLaren DG, Xu G, Nickles RJ, Pyzalski R, DeJesus O, Brown WD.

Neurology

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Rate of decline in 6-L-[(18)F]fluorodopa (FDOPA) uptake within the striatum has been reported as showing regional differences in Parkinson's disease (PD). We acquired longitudinal brain FDOPA positron emission tomography (PET) studies in 26 PD subjects and 11 controls over 4.5 years. We analyzed both spatially normalized voxel-wise maps of radiotracer influx (Kocc) and average Kocc values for six non-overlapping volumes of interest (VOIs) encompassing the striatum. The voxel-wise analysis showed that in PD, FDOPA Kocc decline spanned the striatum but was greatest in the posterior putamen ipsilateral and anterior putamen contralateral to initial symptoms. The VOI approach showed that absolute rates of Kocc decline were significantly greater in PD than control subjects, but that the slope of decline did not differ between subregions. In PD, ratios of uptake between subregions did not change during the study with the exception of the ipsilateral putamen/caudate ratio. Decline rates were marginally greater during earlier time segments. Both male gender and advancing age were associated with lower baseline FDOPA uptake, but no difference in decline rates. VOI Kocc values were significantly correlated with disease duration, but only moderately correlated with clinical measures. We conclude that FDOPA uptake in subregions of the striatum is strongly correlated with disease duration and age, and declines approximately equally from symptom onset in PD. This implies that in idiopathic PD, relative preservation of uptake in the anterior striatum reflects a delay in pathologic involvement of nigrostriatal projections to this region.

Epilepsy Behav. 2011 Apr;20(4):721-4. Epub 2011 Mar 25.

FDG-PET in the diagnosis of complex partial status epilepticus originating from the frontal lobe.

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Complex partial status epilepticus of frontal origin can manifest as nonconvulsive behavioral symptoms that mimic psychiatric illness and, thus, may elude timely diagnosis. The diagnosis can be further delayed by absence of ictal activity on scalp electroencephalography when the ictal origin is orbitofrontal or mesial frontal. We describe the case of a 51-year-old woman with clinically subtle complex partial status epilepticus of left orbitofrontal origin, lacking any clear ictal pattern on the electroencephalogram, who was finally diagnosed using positron emission tomography with [(18)F]fluorodeoxyglucose (FDG-PET). Subsequent FDG-PET following 5 days of oxcarbazepine therapy demonstrated resolution of the left orbitofrontal hypermetabolic focus. FDG-PET is a potentially useful modality for diagnosing nonconvulsive status epilepticus that is not evident on electroencephalography.

BMC Neurol. 2011 Mar 23;11:35.

Subregional 6-[18F]fluoro-L-m-tyrosine uptake in the striatum in Parkinson's disease.

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In idiopathic Parkinson's disease (PD) the clinical features are heterogeneous and include different predominant symptoms. The aim of the present study was to determine the relationship between subregional aromatic L-amino acid decarboxylase (AADC) activity in the striatum and the cardinal motor symptoms of PD using high-resolution positron emission tomography (PET) with an AADC tracer, 6-[18F]fluoro-L-m-tyrosine (FMT). We assessed 101 patients with PD and 19 healthy volunteers. PD was diagnosed based on the UK Brain Bank criteria by two experts on movement disorders. Motor symptoms were measured with the Unified Parkinson's Disease Rating Scale (UPDRS). FMT uptake in the subregions of the striatum was analyzed using semi-automated software for region-of-interest demarcation on co-registered magnetic resonance images. In all PD patients, FMT uptake was decreased in the posterior putamen regardless of predominant motor symptoms and disease duration. Smaller uptake values were found in the putamen contralateral to the side with more affected limbs. The severity of bradykinesia, rigidity, and axial symptoms was correlated with the decrease of FMT uptake in the putamen, particularly in the anterior part. No significant correlation was observed between tremors and FMT uptake. Decrease of FMT uptake in the posterior putamen appears to be most sensitive in mild PD and uptake in the anterior putamen may reflect the severity of main motor symptoms, except for tremor.

Neurology. 2011 Mar 22;76(12):1091-8.

Plasma apolipoprotein E and Alzheimer disease risk: the AIBL study of aging.

Gupta VB, Laws SM, Villemagne VL, Ames D, Bush AI, Ellis KA, Lui JK, Masters C, Rowe CC, Szoek C, Taddei K, Martins RN; AIBL Research Group.

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Neurology

There is mounting evidence for the contribution of apoE to the pathophysiology of Alzheimer disease (AD). Studies also indicate that plasma apoE levels may reflect disease status, suggesting that apoE is a potential AD biomarker. However, while some studies of apoE levels in plasma have presented correlations with AD pathology, others have not. Thus, there is a lack of consensus as to the suitability of plasma apoE as an AD biomarker. The major objective of this cross-sectional study was to investigate total plasma apoE as well as levels of the apoE4 form in a large, highly characterized cohort which included both healthy controls and participants with early-stage AD. Total apoE and apoE4 were measured in 1,079 individuals drawn from the highly characterized Australian Imaging, Biomarkers and Lifestyle (AIBL) study. Total and isoform-specific plasma apoE levels were then compared with cerebral A β load, as assessed by PET using Pittsburgh compound B (PiB). Total apoE and apoE4 levels were found to be significantly lower in patients with AD in the entire cohort, and decrease with A β load in the PiB-PET subset. ApoE levels were significantly lower among ϵ 4 homozygous individuals. In APOE ϵ 3/ ϵ 4 heterozygote carriers, apoE4 levels decrease, indicating that apoE3 levels increase with disease. Analysis of cross-sectional data from the AIBL study indicates that plasma apoE levels are altered in AD and correlate with AD pathology level. The significance of these findings will be determined in the AIBL longitudinal study of aging.

Neurology. 2011 Mar 22;76(12):1046-50.

Cholinergic dysfunction after traumatic brain injury: preliminary findings from a PET study.

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There is evidence that the cholinergic system is frequently involved in the cognitive consequences of traumatic brain injury (TBI). We studied whether the brain cholinergic function is altered after TBI in vivo using PET. Cholinergic function was assessed with [methyl-(11)C]N-methylpiperidyl-4-acetate, which reflects the acetylcholinesterase (AChE) activity, in 17 subjects more than 1 year after a TBI and in 12 healthy controls. All subjects had been without any centrally acting drugs for at least 4 weeks. The AChE activity was significantly lower in subjects with TBI compared to controls in several areas of the neocortex (-5.9% to -10.8%, $p=0.053$ to 0.004). Patients with chronic cognitive symptoms after TBI show widely lowered AChE activity across the neocortex.

J Cereb Blood Flow Metab. 2011 Jun;31(6):1493-500. Epub 2011 Mar 9.

Crossed cerebellar diaschisis after stroke: can perfusion-weighted MRI show functional inactivation?

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In this study, we aimed to assess the detection of crossed cerebellar diaschisis (CCD) following stroke by perfusion-weighted magnetic resonance imaging (PW-MRI) in comparison with positron emission tomography (PET). Both PW-MRI and 15O-water-PET were performed in acute and subacute hemispheric stroke patients. The degree of CCD was defined by regions of interest placed in the cerebellar hemispheres ipsilateral (I) and contralateral (C) to the supratentorial lesion. An asymmetry index ($AI=C/I$) was calculated for PET-cerebral blood flow (CBF) and MRI-based maps of CBF, cerebral blood volume (CBV), mean transit time (MTT), and time to peak (TTP). The resulting AI values were compared by Bland-Altman (BA) plots and receiver operating characteristic analysis to detect the degree and presence of CCD. A total of 26 imaging

procedures were performed (median age 57 years, 20/26 imaged within 48 hours after stroke). In BA plots, all four PW-MRI maps could not

reliably reflect the degree of CCD. In receiver operating characteristic analysis for detection of CCD, PW-CBF performed poorly (accuracy 0.61),

whereas CBV, MTT, and TTP failed (accuracy <0.60). On the basis of our findings, PW-MRI at 1.5 T is not suited to depict CCD after stroke.

Seizure. 2011 Jun;20(5):425-7. Epub 2011 Mar 3.

How to effectively constraint the cost of presurgical evaluation for resective surgery in low-income population: clinically oriented opinions.

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Neurology

Epilepsy surgery plays a pivotal role in the successful treatments of intractable epilepsy. In China, economic burden for epileptic patients is heavy. Because of limited economic resources, appropriate utilization of presurgical evaluation technologies is especially important for low-income patients, who could benefit from surgery. This study proposed the strategies for restricting the cost of presurgical evaluation for resective surgery in low-income population with refractory epilepsy. A retrospective study was performed on the database of patients with resective surgery from January 2007 to June 2009 in West China Hospital of Sichuan University. Presurgical evaluation technologies and outcome were analyzed. As a result, 143 patients underwent resective operation were included in this study. Seizure free can be reached at 63.8% patients with (ATL) and 61.1% with focal lesionectomy (FLE). Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS), positron emission tomography (PET), routine electroencephalography (REEG), video-EEG (VEEG) and invasive-EEG (IEEG) were used for investigation. The cost of those technologies was listed for consultation. Based on these findings, how to make the proper choice for surgery candidates was suggested according to different types of epilepsy.

Neurology. 2011 Apr 12;76(15):1322-9. Epub 2011 Mar 2.

fMRI language dominance and FDG-PET hypometabolism.

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Atypical language dominance is common in patients with temporal lobe epilepsy. We examined the association of left temporal hypometabolism with laterality of fMRI activation in a language task in a cross-sectional study. Thirty patients with temporal lobe epilepsy (mean age 32.4 ± 11.0 years [range 18-55]; epilepsy onset 15.3 ± 11.3 years [range 0.8-40]; 22 left focus, 8 right focus) had (18)fluoro-deoxyglucose (FDG)-PET using noninvasive cardiac input function. After MRI-based partial volume correction, regional glucose metabolism (CMR_{glc}) was measured and asymmetry index, $AI = 2(l - R)/(L + R)$, calculated. fMRI language dominance was assessed with an auditory definition decision paradigm at 3 T. fMRI data were analyzed in SPM2 using regions of interest from Wake Forest PickAtlas (Wernicke area [WA], inferior frontal gyrus [IFG], middle frontal gyrus [MFG]) and bootstrap laterality index, $LI = (l - R/L + R)$. Nineteen patients had ipsilateral temporal hypometabolism; 3 of 4 patients with atypical language had abnormal FDG-PET. Increasing left midtemporal hypometabolism correlated with decreased MFG LI ($r = -0.41$, $p < 0.05$) and showed trends with WA LI ($r = -0.37$, $p = 0.055$) and IFG LI ($r = -0.31$, $p = 0.099$); these relationships became more significant after controlling for age at onset. Increasing hypometabolism was associated with fewer activated voxels in WA ipsilateral to the focus and more activated voxels contralaterally, but overall, activation amount in left WA was similar to subjects without left temporal hypometabolism ($t = -1.39$, $p > 0.10$). We did not find evidence of impaired blood oxygenation level-dependent response in hypometabolic cortex. Regional hypometabolism appears to be a marker for the temporal lobe dysfunction that leads to displacement of language function.

J Cereb Blood Flow Metab. 2011 Jun;31(6):1475-81. Epub 2011 Mar 2.

Age and sex effects on 5-HT(4) receptors in the human brain: a [(11)C]SB207145 PET study.

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Experimental studies indicate that the 5-HT(4) receptor activation influence cognitive function, affective symptoms, and the development of Alzheimer's disease (AD). The prevalence of AD increases with aging, and women have a higher predisposition to both AD and affective disorders than men. This study aimed to investigate sex and age effects on 5-HT(4) receptor-binding potentials in striatum, the limbic system, and neocortex. Positron-emission tomographic scans were conducted using the radioligand [(11)C]SB207145 in a cohort of 30 healthy subjects (mean age 44 years; range 20 to 86 years; 14 men and 16 women). The output parameter, BP(ND), was modeled using the simplified reference tissue model, and partial volume correction was performed with the Muller-Gartner method. A decline with age of 1% per decade was found only in striatum. Women had a 13% lower 5-HT(4) receptor binding in the limbic system. The lower limbic 5-HT(4) receptor binding in women supports a role for 5-HT(4) receptors in the sex-specific differences in emotional control and might contribute to the higher prevalence of affective diseases and AD in women. The relatively stable 5-HT(4) receptor binding with aging contrasts others in subtypes of receptors, which generally decrease with aging.

Sleep. 2011 Mar 1;34(3):341-7.

The dopamine transporter is decreased in the striatum of subjects with restless legs syndrome.

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Prior studies, all using SPECT techniques, failed to find any differences for dopamine transporter (DAT) in restless legs syndrome (RLS) subjects. The distinct pharmacokinetic properties associated with SPECT-determined DAT along with rapid biodynamic changes in DAT may,

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however, have missed membrane-bound DAT differences. The current studies assessed real-time DAT binding potentials (BP) in striatum of RLS patients using (11)C-methylphenidate and PET techniques. RLS medications were stopped at least 11 days prior to the PET study. Clinical severity of RLS was also assessed. PET scans were performed at 2 different times of day (starting at 08:30 and 19:30) in separate groups of subjects. The primary outcome measure was total striatal DAT BP. Thirty-six patients with primary RLS and 34 age- and gender-matched controls. RLS subjects had significantly lower DAT binding in the striatum compared to controls on both the Day and the Night scans. DAT was decreased in putamen and caudate but not the ventral striatum of RLS subjects. There were no diurnal differences in DAT for the total group or for control and RLS separately. DAT BP did not correlate with any clinical measures of RLS. The current study found a significant decrease in DAT BP in two independent studies. These results when viewed along with prior RLS SPECT and autopsy studies of DAT, and cell culture studies with iron deficiency and DAT, suggest that membrane-bound striatal DAT, but not total cellular DAT, may be decreased in RLS.

BMC Neurol. 2011 Feb 24;11:25.

Central modulation in cluster headache patients treated with occipital nerve stimulation: an FDG-PET study.

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Occipital nerve stimulation (ONS) has raised new hope for drug-resistant chronic cluster headache (drCCH), a devastating condition. However its mode of action remains elusive. Since the long delay to meaningful effect suggests that ONS induces slow neuromodulation, we have searched for changes in central pain-control areas using metabolic neuroimaging. Ten drCCH patients underwent an 18FDG-PET scan after ONS, at delays varying between 0 and 30 months. All were scanned with ongoing ONS (ON) and with the stimulator switched OFF. After 6-30 months of ONS, 3 patients were pain free and 4 had a $\geq 90\%$ reduction of attack frequency (responders). In all patients compared to controls, several areas of the pain matrix showed hypermetabolism: ipsilateral hypothalamus, midbrain and ipsilateral lower pons. All normalized after ONS, except for the hypothalamus. Switching the stimulator ON or OFF had little influence on brain glucose metabolism. The perigenual anterior cingulate cortex (PACC) was hyperactive in ONS responders compared to non-responders. Metabolic normalization in the pain neuromatrix and lack of short-term changes induced by the stimulation might support the hypothesis that ONS acts in drCCH through slow neuromodulatory processes. Selective activation in responders of PACC, a pivotal structure in the endogenous opioid system, suggests that ONS could restore balance within dysfunctioning pain control centres. That ONS is nothing but a symptomatic treatment might be illustrated by the persistent hypothalamic hypermetabolism, which could explain why autonomic attacks may persist despite pain relief and why cluster attacks recur shortly after stimulator arrest. PET studies on larger samples are warranted to confirm these first results.

PLoS One. 2011 Feb 8;6(2):e16775.

Human stiff-person syndrome IgG induces anxious behavior in rats.

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Anxiety is a heterogeneous behavioral domain playing a role in a variety of neuropsychiatric diseases. While anxiety is the cardinal symptom in disorders such as panic disorder, co-morbid anxious behavior can occur in a variety of diseases. Stiff person syndrome (SPS) is a CNS disorder characterized by increased muscle tone and prominent agoraphobia and anxiety. Most patients have high-titer antibodies against glutamate decarboxylase (GAD) 65. The pathogenic role of these autoantibodies is unclear. We re-investigated a 53 year old woman with SPS and profound anxiety for GABA-A receptor binding in the amygdala with (11)C-flumazenil PET scan and studied the potential pathogenic role of purified IgG from her plasma filtrates containing high-titer antibodies against GAD 65. We passively transferred the IgG fraction intrathecally into rats and analyzed the effects using behavioral and in vivo electrophysiological methods. In cell culture, we measured the effect of patient IgG on GABA release from hippocampal neurons. Repetitive intrathecal application of purified patient IgG in rats resulted in an anxious phenotype resembling the core symptoms of the patient. Patient IgG selectively bound to rat amygdala, hippocampus, and frontal cortical areas. In cultured rat hippocampal neurons, patient IgG inhibited GABA release. In line with these experimental results, the GABA-A receptor binding potential was reduced in the patient's amygdala/hippocampus complex. No motor abnormalities were found in recipient rats. The observations in rats after passive transfer lead us to propose that anxiety-like behavior can be induced in rats by passive transfer of IgG from a SPS patient positive for anti-GAD 65 antibodies. Anxiety, in this case, thus may be an antibody-mediated phenomenon with consecutive disturbance of GABAergic signaling in the amygdala region.

NeuroRehabilitation. 2011;28(1):3-14.

Disorders of consciousness: what's in a name?

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Following a coma, some patients may "awaken" without voluntary interaction or communication with the environment. More than 40 years ago this condition was coined coma vigil or apallic syndrome and later became worldwide known as "persistent vegetative state". About 10 years ago it became clear that some of these patients who failed to recover verbal or non-verbal communication did show some degree of consciousness--a condition called "minimally conscious state". Some authors questioned the usefulness of differentiating unresponsive "vegetative" from minimally conscious patients but subsequent functional neuroimaging studies have since objectively demonstrated differences in residual cerebral processing and hence, we think, conscious awareness. These neuroimaging studies have also demonstrated that a small subset of unresponsive "vegetative" patients may show unambiguous signs of consciousness and command following inaccessible to bedside clinical examination. These findings, together with negative associations intrinsic to the term "vegetative state" as well as the diagnostic errors and their potential effect on the treatment and care for these patients gave rise to the recent proposal for an alternative neutral and more descriptive name: unresponsive wakefulness syndrome. We here give an overview of PET and (functional) MRI studies performed in these challenging patients and stress the need for a separate ICD-9-CM diagnosis code and MEDLINE MeSH entry for "minimally conscious state" as the lack of clear distinction between vegetative state/unresponsive wakefulness syndrome and minimally conscious state may encumber scientific studies in the field of disorders of consciousness.

Neurology. 2011 Mar 22;76(12):1085-90. Epub 2011 Feb 16.

Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study.

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Patients with amnesic mild cognitive impairment (MCI) have greater risk of conversion to Alzheimer disease (AD). Increased brain amyloid burden in AD and MCI has been demonstrated with PET using [(11)C] Pittsburgh compound B (PiB) as a tracer. To evaluate change in β -amyloid deposition in with MCI during 2-year follow-up. Patients with MCI and controls were studied with [(11)C] PiB PET, MRI, and neuropsychometry at baseline and these investigations were repeated in patients with MCI after follow-up. Those patients with MCI converting to AD during follow-up had greater [(11)C] PiB retention in the posterior cingulate ($p=0.020$), in the lateral frontal cortex ($p=0.006$), in the temporal cortex ($p=0.022$), in the putamen ($p=0.041$), and in the caudate nucleus ($p=0.025$) as compared to nonconverters. In converters, there was no significant change in [(11)C] PiB uptake, whereas an increase was seen as compared to baseline in nonconverters in the anterior and posterior cingulate, temporal and parietal cortices, and putamen. Hippocampal atrophy was greater in converters at baseline than in nonconverters, but increased significantly in both groups during follow-up. Hippocampal atrophy and amyloid deposition seem to dissociate during the evolution of MCI, the atrophy increasing clearly and [(11)C] PiB retention changing modestly when conversion to AD occurs. Longer follow-up is needed to determine whether nonconverters would convert to AD later, which would suggest accelerated [(11)C] PiB retention preceding clinical conversion.

Neuroscientist. 2011 Aug;17(4):368-81. Epub 2011 Feb 10.

Transcranial magnetic stimulation at the interface with other techniques: a powerful tool for studying the human cortex.

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Transcranial magnetic stimulation (TMS) has developed into a very powerful tool in the hands of basic and clinical neuroscientists alike to study function and dysfunction of the human brain noninvasively and painlessly. However, as a stand-alone technique, the potential of TMS to gain knowledge is relatively limited. This potential can be strongly enhanced by combining TMS with simultaneous measurements in other electrophysiological (EEG) or imaging modalities (PET, fMRI, NIRS, MRS) or by combining TMS with exposure to neuroactive drugs (pharmaco-TMS). This review provides an up-to-date synopsis of these combined approaches and highlights important examples that have advanced our understanding of how TMS interacts with neuronal networks in the human brain.

Neurology. 2011 Mar 15;76(11):944-52. Epub 2011 Feb 9.

Abnormal metabolic brain networks in Tourette syndrome.

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To identify metabolic brain networks that are associated with Tourette syndrome (TS) and comorbid obsessive-compulsive disorder (OCD). We utilized [(18)F]-fluorodeoxyglucose and PET imaging to examine brain metabolism in 12 unmedicated patients with TS and 12 age-matched controls. We utilized a spatial covariance analysis to identify 2 disease-related metabolic brain networks, one associated with TS in general (distinguishing TS subjects from controls), and another correlating with OCD severity (within the TS group alone). Analysis of the combined

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group of patients with TS and healthy subjects revealed an abnormal spatial covariance pattern that completely separated patients from controls ($p < 0.0001$). This TS-related pattern (TSRP) was characterized by reduced resting metabolic activity of the striatum and orbitofrontal cortex associated with relative increases in premotor cortex and cerebellum. Analysis of the TS cohort alone revealed the presence of a second metabolic pattern that correlated with OCD in these patients. This OCD-related pattern (OCDRP) was characterized by reduced activity of the anterior cingulate and dorsolateral prefrontal cortical regions associated with relative increases in primary motor cortex and precuneus. Subject expression of OCDRP correlated with the severity of this symptom ($r = 0.79$, $p < 0.005$). These findings suggest that the different clinical manifestations of TS are associated with the expression of 2 distinct abnormal metabolic brain networks. These, and potentially other disease-related spatial covariance patterns, may prove useful as biomarkers for assessing responses to new therapies for TS and related comorbidities.

Neurol Sci. 2011 Feb 5. [Epub ahead of print]

Two cases of dementias with motor neuron disease evaluated by Pittsburgh compound B-positron emission tomography.

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We described the cases of two patients with dementia associated with motor neuron disease, the former with frontotemporal dementia (FTD) and the latter with Alzheimer's disease (AD), studied by the Pittsburgh compound B-positron emission tomography (PIB-PET). In the FTD patient, the PIB-PET revealed no amyloid accumulation in the cortex, whilst in the AD patient showed amyloid accumulation mainly in the frontal, parietal and lateral temporal lobes, besides the posterior cingulate gyrus and the precuneus. Thus, PIB-PET might facilitate the discrimination of different proteinopathies that cause neurodegenerative diseases, as dementia associated with ALS.

Neuropathology. 2011 Jan 27. doi: 10.1111/j.1440-1789.2010.01193.x. [Epub ahead of print]

An immunohistochemical study of the serotonin 1A receptor in the hippocampus of subjects with Alzheimer's disease.

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Alzheimer's disease (AD) is associated with neuronal degeneration, synaptic loss and deficits in multiple neurotransmitter systems. Alterations in the serotonin 1A (5-HT_{1A}) receptor can contribute to impaired cognitive function in AD, and both in vitro binding and Positron emission tomography (PET) imaging studies have demonstrated that 5-HT_{1A} receptors in the hippocampus/medial temporal cortex are affected early in AD. This neuropathological study examined the localization and immunoreaction intensity of 5-HT_{1A} receptor protein in AD hippocampus with the goal to determine whether neuronal receptor levels are influenced by the severity of NFT severity defined by Braaks' pathological staging and to provide immunohistochemical confirmation of the binding assays and PET imaging studies. Subjects included AD patients and non-AD controls (NC) stratified into three Braaks' stages (Braak 0-II, NC; Braak III/IV and V/VI, AD). In the Braak 0-II group, 5-HT_{1A}-immunoreactivity (ir) was prominent in the neuropil of the CA1 and subiculum, moderate in the dentate gyrus molecular layer (DGml), and low in the CA3 and CA4. No changes in 5-HT_{1A}-ir were observed in the hippocampus of AD subjects in the Braak III/IV group. Hippocampal 5-HT_{1A}-ir intensity was markedly decreased in the CA1 region in 6/11 (54.5%) subjects in the Braak V/VI group. Across all three groups combined, there was a statistically significant association between reduced 5HT_{1A}-ir and neuronal loss in the CA1, but not in the CA3. The present data demonstrate that hippocampal 5-HT_{1A} receptors are mainly preserved until the end-stage of NFT progression in AD. Thus, the utility of PET imaging using a 5-HT_{1A}-specific radiolabeled probe as a marker of hippocampal neuronal loss may be limited to the CA1 field in advanced stage AD cases

Epilepsy Behav. 2011 Feb;20(2):194-208. Epub 2011 Jan 22.

Presurgical epilepsy localization with interictal cerebral dysfunction.

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Localization of interictal cerebral dysfunction with 2-[(18)F]fluoro-2-D-deoxyglucose (FDG) positron emission tomography (PET) and neuropsychological examination usefully supplements electroencephalography (EEG) and brain magnetic resonance imaging (MRI) in planning epilepsy surgery. In MRI-negative mesial temporal lobe epilepsy, correlation of temporal lobe hypometabolism with extracranial ictal EEG can support resection without prior intracranial EEG monitoring. In refractory localization-related epilepsies, hypometabolic sites may supplement other data in hypothesizing likely ictal onset zones in order to intracranial electrodes for ictal recording. Prognostication of postoperative seizure

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freedom with FDG PET appears to have greater positive than negative predictive value. Neuropsychological evaluation is critical to evaluating the potential benefit of epilepsy surgery. Cortical deficits measured with neuropsychometry are limited in lateralizing and localizing value for determination of ictal onset sites, however. Left temporal resection risks iatrogenic verbal memory deficits and dysnomia, and neuropsychological findings are useful in predicting those at greatest risk. Prognostication of cognitive risks with resection at other sites is less satisfactory.

J Neuroimaging. 2011 Jan 11. doi: 10.1111/j.1552-6569.2010.00572.x. [Epub ahead of print]

Imaging Inflammation in a Patient with Epilepsy Due to Focal Cortical Dysplasia.

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Evidence from animal models and examination of human epilepsy surgery specimens indicates that inflammation plays an important role in epilepsy. Positron emission tomography (PET) using [C11]PK11195, a marker of activated microglia, provides a means to visualize neuroinflammation in vivo in humans. We hypothesize that in patients with active epilepsy, [C11]PK11195 PET (PK-PET) may be able to identify areas of focally increased inflammation corresponding to the seizure onset zone. A young woman with intractable epilepsy underwent PK-PET as part of an approved research study. PK-PET results were compared with results from other clinical studies. PK-PET revealed an area of focally increased radiotracer uptake in the right frontal lobe corresponding to this patient's seizure focus as identified by ictal and interictal 18F-fluorodeoxyglucose (FDG)-PET and EEG. Routine brain magnetic resonance imaging (MRI) was initially considered normal, though high-resolution studies showed possible subtle dysplasia of the right frontal lobe. The patient underwent a right frontal lobe resection, and pathological evaluation showed focal cortical dysplasia with activated microglia. PK-PET can identify neuroinflammation associated with subtle focal cortical dysplasia, and may therefore have a clinical role in guiding epilepsy surgery for patients with difficult-to-localize seizure foci.

J Neuroimaging. 2011 Jan 11. doi: 10.1111/j.1552-6569.2010.00565.x. [Epub ahead of print]

Increased L-[1-(11) C] Leucine Uptake in the Leptomeningeal Angioma of Sturge-Weber Syndrome: A PET Study.

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We used L-[1-(11) C]leucine (LEU) positron emission tomography (PET) to measure amino acid uptake in children with Sturge-Weber syndrome (SWS), and to relate amino acid uptake measures with glucose metabolism. LEU and 2-deoxy-2[(18) F]fluoro-D-glucose (FDG) PET were performed in 7 children (age: 5 months-13 years) with unilateral SWS. Asymmetries of LEU uptake in the posterior brain region, underlying the angioma and in frontal cortex, were measured and correlated with glucose hypometabolism. Kinetic analysis of LEU uptake was performed in 4 patients. Increased LEU standard uptake value (SUV, mean: 15.1%) was found in the angioma region in 6 patients, and smaller increases in LEU SUV (11.5%) were seen in frontal cortex in 4 of the 6 patients, despite normal glucose metabolism in frontal regions. High LEU SUV was due to both increased tracer transport (3/4 patients) and high protein synthesis rates (2/4). FDG SUV asymmetries in the angioma region were inversely related to LEU SUV asymmetries ($r = -.83$, $P = .042$). Increased amino acid uptake in the angioma region and also in less affected frontal regions may provide a marker of pathological mechanisms contributing to chronic brain damage in children with SWS.

Neurology. 2011 Jan 4;76(1):41-8.

Multimodality imaging in the surgical treatment of children with nonlesional epilepsy.

Seo JH, Holland K, Rose D, Rozhkov L, Fujiwara H, Byars A, Arthur T, DeGrauw T, Leach JL, Gelfand MJ, Miles L, Mangano FT, Horn P, Lee KH.

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To evaluate the diagnostic value of individual noninvasive presurgical modalities and to study their role in surgical management of nonlesional pediatric epilepsy patients. We retrospectively studied 14 children (3-18 years) with nonlesional intractable focal epilepsy. Clinical

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characteristics, surgical outcome, localizing features on 3 presurgical diagnostic tests (subtraction peri-ictal SPECT coregistered to MRI [SISCOM], statistical parametric mapping [SPM] analysis of [18F] FDG-PET, magnetoencephalography [MEG]), and intracranial EEG (iEEG) were reviewed. The localization of each individual test was determined for lobar location by visual inspection. Concordance of localization between each test and iEEG was scored as follows: 2=lobar concordance; 1=hemispheric concordance; 0=discordance or nonlocalization. Total concordance score in each patient was measured by the summation of concordance scores for all 3 tests. Seven (50%) of 14 patients were seizure-free for at least 12 months after surgery. One (7%) had only rare seizures and 6 (43%) had persistent seizures. MEG (79%, 11/14) and SISCOM (79%, 11/14) showed greater lobar concordance with iEEG than SPM-PET (13%, 3/14) ($p<0.05$). SPM-PET provided hemispheric lateralization (71%, 10/14) more often than lobar localization. Total concordance score tended to be greater for seizure-free patients (4.7) than for non-seizure-free patients (3.9). Our data suggest that MEG and SISCOM are better tools for lobar localization than SPM analysis of FDG-PET in children with nonlesional epilepsy. A multimodality approach may improve surgical outcome as well as selection of surgical candidates in patients without MRI abnormalities.

Parkinsonism Relat Disord. 2011 Mar;17(3):160-5. Epub 2010 Dec 31.

Amyloid and glucose imaging in dementia with Lewy bodies and multiple systems atrophy.

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Multiple Systems Atrophy (MSA) and Dementia with Lewy bodies (DLB) can present with both REM behavior disorder and severe autonomic dysfunction. In rare occasions, patients with MSA progress to cognitive impairment and even dementia. Positron emission topography (PET) imaging using both the amyloid ligand Pittsburgh Compound B (11C-PiB) and 18 flurodeoxyglucose (18F-FDG) was used to ascertain the presence of amyloid and pattern of glucose metabolic derangement in both disorders. Patients diagnosed with probable DLB or MSA, with clinical symptoms of either REM Behavior Disorder (RBD), Parkinsonism, or dysautonomia were prospectively identified. All underwent both 11C-PiB and 18F-FDG PET imaging. Statistical comparison between DLB, MSA, and normal controls was performed. Six patients, 3 with DLB, 2 with Parkinson predominant MSA (MSA-P), and 1 with cerebellar predominant MSA (MSA-C) were identified. Increased level of PiB retention was noted in all patients diagnosed with DLB, but was absent in MSA. In those with DLB, glucose hypometabolism corresponded with regions of amyloid presence, and included prefrontal, parietotemporal, occipital and primary visual cortex regions. MSA patients were distinguished by cerebellar glucose hypometabolism. These findings emphasize the distinguishing characteristics between the alpha-synuclein related disorders of DLB and MSA. The absence of amyloid in the cases of MSA is a possible distinguishing characteristic of the disorder.

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Imaging expression of the human somatostatin receptor subtype-2 reporter gene with 68Ga-DOTATOC.

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The human somatostatin receptor subtype 2 (hSSTR2)-68Ga-DOTATOC reporter system has several attractive features for potential translation to human studies. These include a low expression of hSSTR2 in most organs, a rapid internalized accumulation of 68Ga-DOTATOC in the SSTR2-expressing cells, and a rapid excretion of unbound radioligand by the renal system. We performed a series of in vitro and in vivo validation studies of this reporter system. A retroviral vector containing a dual reporter, pQCXhSSTR2-IRES-GFP (IRES: internal ribosome entry site; GFP: green fluorescent protein), was constructed and transduced into Jurkat, C6, and U87 cells. Stably transduced reporter cells were characterized in vitro using optical and radiometric methods. Multiple tumor-bearing mice were evaluated with 68Ga-DOTATOC PET studies. The dual-reporter genes were incorporated into all tumor cell lines, and their expression levels were confirmed by fluorescence-activated cell sorting (FACS), GFP visualization, and reverse-transcriptase polymerase chain reaction (RT-PCR) analysis for hSSTR2. In vitro, hSSTR2 cell membrane expression was 36,000, 280,000, and 1,250,000 copies per cell for the SSTR2-transfected Jurkat, U87, and C6 cell lines. Small-animal PET of 68Ga-DOTATOC in tumor-bearing mice demonstrated that the in vivo uptake of this radioligand was directly proportional to the in vitro expression of hSSTR2. The in vivo uptake of 68Ga-DOTATOC, at 2 h after injection, was low in all organs except the kidneys (7.8 percentage of injected dose per gram [%ID/g]) and as high as 15.2 %ID/g in transduced C6 tumors. The corresponding transduced-to-nontransduced tumor uptake ratio was 64, and the tumor-to-muscle uptake ratio was around 500. 68Ga-DOTATOC is an excellent specific ligand for this hSSTR2 reporter system and for hSSTR2 reporter gene PET. Because DOTATOC has undergone extensive clinical testing, this human reporter system has the potential for translation to human studies.
