Preclinical Applications for High-Precision, Simultaneous Molecular and Functional PET/MRI Imaging *in vivo*

Dr. John Saunders, CSO Cubresa

ABSTRACT

Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are highly complementary, clinically translatable modalities for understanding disease mechanisms and testing novel treatments in small animal subjects.

Preclinical researchers are identifying applications benefitting from simultaneous PET/MRI in areas such as neuroscience and cardiovascular disease. After receptor agonist administration, simultaneous PET-fMRI has been used to correlate neurovascular response and dopamine D2/D3R occupancy in non-human primates. In mice, simultaneous FDG-PET and DWI evaluated the rapidly changing time course of a hypoxic challenge in models of cerebral hypoxia-ischemia. And mouse models of myocardial infarction have been successfully studied using multi-parametric MRI data sets coupled with PET-based assessment of cell viability.

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ABOUT THE AUTHOR

Dr. John Saunders has over 40 years experience in the science and technology realm, in particular with MRI imaging technology. John was the original CEO and then CSO of IMRIS, and one of the inventors of the original intraoperative MRI scanner. He spent 15 years as a university professor/researcher, 13 years as a researcher at the NRC Canada, and has over 400 peer-reviewed publications as well as 6 granted US patents and 12 US patents pending.

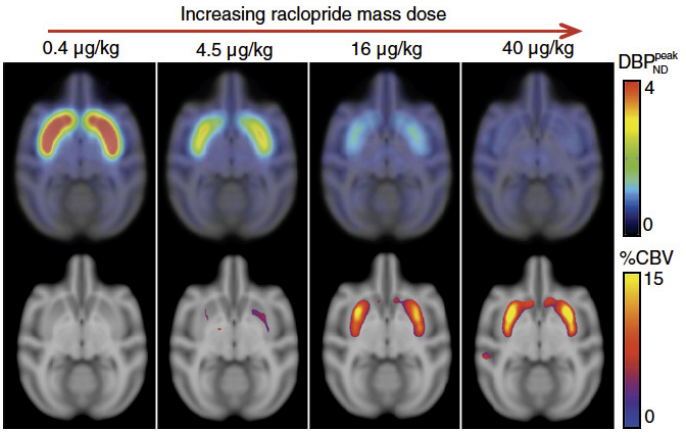

Figure 1. From Sander, et al. 2013[3]: (Upper) DBP^{peak}_{ND} parameter maps from PET data, overlaid on an anatomical MR atlas. (Lower) Maps of $\%CBV^{peak}$ change from fMRI data, windowed by a P-value map with P<0.03. All maps are created from data from two animals with a mixed-effects model. Similarities in the spatial distribution of PET and fMRI signals and the dose dependencies support the idea that antagonism of RAC at D2/D3R is elicited by the CBV changes.

SIMULTANEOUS MEASUREMENT OF NEUROCHEMICAL AND NEUROVASCULAR CHANGES TO MORE PRECISELY AND ACCURATELY MODEL BRAIN ACTIVITY

Both PET and MRI scanning have been used for neuroimaging[1]. However, with the advent of instruments capable of simultaneous PET-MRI, these complementary techniques allow researchers to better correlate changes in brain chemistry with changes in brain activity.

For example, a recent study by researchers from Massachusetts General Hospital, MIT, the University of Copenhagen, and Katholieke Universiteit in Leuven employed simultaneous PET and functional MRI (PET-fMRI) to measure neurovascular response when administering pharmacologic doses of a receptor agonist while at the same time measuring dopamine D2/D3R occupancy in basal ganglia of non-human primates[2].

The results showed strong correlation between neurovascular response and dopamine receptor binding across a wide dynamic range and demonstrate the usefulness of concurrent assessment of hemodynamics and receptor-specific neurotransmission in preclinical and clinical studies.

PET emission data offers high sensitivity and neurochemical specificity, while fMRI offers high spatio-temporal resolution for visualizing changes in neurovascular activity[3]. But more than the fusion of separate molecular and anatomical information, simultaneous PET-fMRI acquisition enables stronger conclusions about cause and effect to be made, since the images are gathered at the same time and under identical physiologic conditions.

Prior to this study, little or no reporting had been done on comparing the functional output measured by fMRI and changes to the neuro-receptor system target by a specific ligand. The

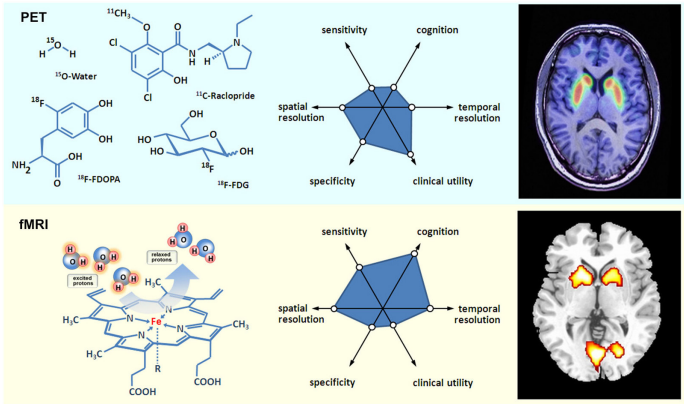

Figure 2. From Mier 2015[4]: Basic aspects of PET (top row) and MRI (bottom row). Left to right: Chemical structures of common PET radiotracers and the induction of relaxation of hemoglobin utilized by MRI, inherent characteristics of PET and MRI, and typical PET overlay onto MRI and MRI images.

authors suppose that this absence of published work is due to the lack of suitable instrumentation such as a combined PET-fMRI system for simultaneous quantitative imaging. The availability of instruments capable of simultaneous PET-fMRI offers the potential for non-invasive assessment of the relative differences in basal neurotransmitter occupancy across regions of the brain and ultimately across subject groups.

Beyond this particular application, indeed there are many other applications where simultaneous imaging is also essential. Measuring cerebral or vascular blood flow, for instance, where physiologic functions vary over time and sequential images will be non-correlated.

Another significant benefit to having both PET and MRI datasets gathered at the same time is the ability to more accurately calculate of volumes using MRI-based Partial-Volume Correction (PVC). The higher-resolution MRI images can be used as a basis for calculating and displaying a more precise and detailed PET image[4].

The technique of simultaneous PET-MRI offers numerous benefits where the sum appears to be much more than the individual parts. Fused PET-MRI data and images gathered simultaneously could enable the realization of a more accurate model of brain activity than with PET and MRI data and images gathered separately.

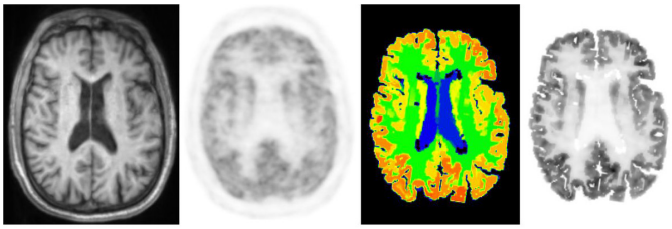

Figure 3. From Catana 2012[5]: The relatively low resolution of PET scans can lead to inaccurate estimations of volume due to Partial Volume Effects (PVE). However, thanks to the superior structural detail provided by MRI, and the elimination of registration problems because of simultaneous PET-MRI image acquisition, recovery coefficients can result in PET data with far greater detail and more accurate tissue activity concentrations.

ACCURATE MULTIMODAL CHARACTERIZATION OF RAPID PHYSIOLOGICAL CHANGES FOLLOWING INDUCED HYPOXIC-ISCHEMIC STROKE ONSET

PET and MRI have been used to study stroke in small animal models, examining changes in water diffusion and glucose metabolism. Ischemic events produce a cascade of rapidly evolving physiological changes[5] that can be highly individualized in certain animal models, creating data interpretation challenges when animals are imaged sequentially. With instruments capable of simultaneous PET/MRI acquisition, researchers can assess complimentary information about the evolution of injury and the effect of interventions such as neuroprotective compounds.

MRI has been used extensively to monitor water diffusion changes in stroke patients, quantified by the apparent diffusion coefficient (ADC) using diffusion weighted imaging (DWI). PET provides complimentary information for evaluating changes in glucose metabolism.

Recently a group of researchers from the University of California, Davis and Genentech demonstrated successful multi-modal evaluation of the time course of a hypoxic challenge in mouse models of cerebral hypoxia-ischemia[6]. The extent of brain injury is variable in these models[7], and along with the speed of ischemic changes, make a strong argument for simultaneous PET/MRI acquisition.

After common carotid artery ligation, anatomical MRI images were obtained followed by dynamic DWI and PET acquisitions capturing the initiation of the hypoxic challenge and subsequent time points. The results demonstrate the time-dependent percent differences in the ADC between the non-occluded and occluded sides of the brain. As has been shown elsewhere, ADC values on the occluded side of the brain decreased as the injury progressed.

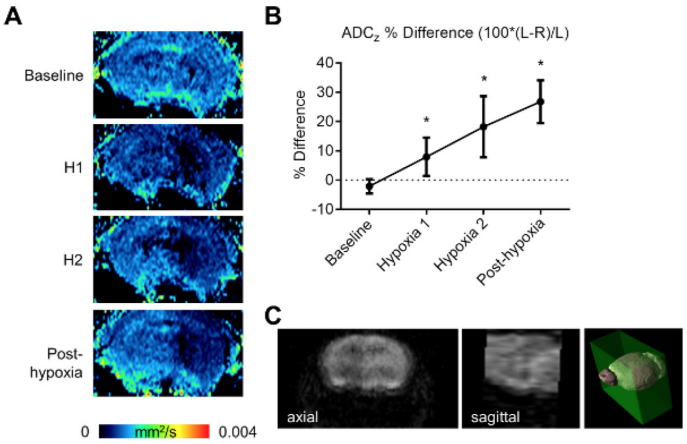

Figure 4. from Ouyang et al. 2016[7]. Example of parametric ADCz maps acquired at baseline and through post-hypoxia. (B) Plot showing %L-R difference in ADCz from baseline to post-hypoxia. Asterisks indicate a significant difference ($p < 0.05$, unpaired t-test) compared to baseline value. Error bars represent +/- one standard deviation. (C) Example of an EPI-DWI acquisition (axial, sagittal, and 3D views to show extent of the FOV).

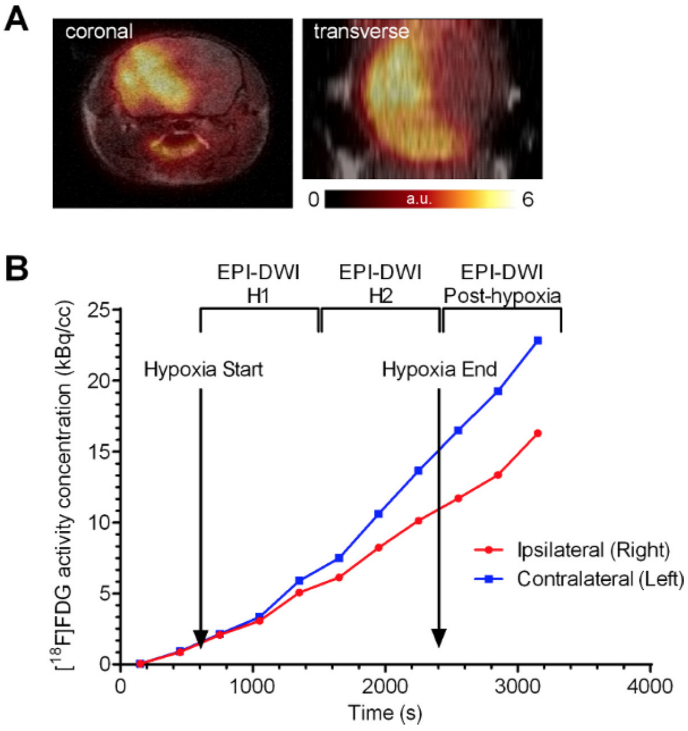

Figure 5. from Ouyang et al. 2016[7]. (A) Coronal and transverse slice of an animal showing [18F]FDG uptake. The PET image is in the foreground and is registered and fused with an anatomical MRI image in the background for visualization. The PET data are summed across all frames. (B) In the same animal,[18F]FDG time activity curve for the contralateral hemisphere (blue) and ipsilateral hemisphere (red).

In most animals, [18F]FDG PET images fused with anatomical MRI images showed reduced tracer uptake in the occluded side relative to the non-occluded side, although this was not true in all cases likely due to animal variability.

These results illustrate the value of simultaneous PET/MRI instrumentation for small animal stroke research. Executing sequential imaging studies and relying on software co-registration techniques would require the assumption that animal physiology has not significantly changed between imaging sessions; a potential pitfall given the rapid progression of ischemic brain injury.

Simultaneous PET/MRI instrumentation can arm researchers with a new, powerful tool for multi-modal investigation into physiological changes during stroke and the effectiveness of novel interventional strategies.

ENHANCED DATA QUALITY DURING MULTIPARAMETRIC EVALUATION OF MYOCARDIAL INFARCTION

Heart failure (HF) is a common condition that develops after the heart becomes damaged or weakened by disease, including conditions such as myocardial infarction. In animal models, human heart failure is mimicked by causing myocardial infarction in the heart, and this can then be used to develop technologies to extend the life of the animal which can then be transitioned to humans.

Damage and recovery can be assessed on the cellular, tissue, organ or whole animal scale but these are rarely measured in concert. Ideally, recovery can be measured on long term studies of animals following the infarction with imaging techniques that monitor these scales simultaneously.

The combination of simultaneous PET and MRI present a combination of four complementary measures of heart function on multiple levels. Standard volumetric measurements of ventricle size at each phase of the heart (cine MRI) can be used to measure end-systolic and end-diastolic volumes (ESV, EDV respectively). The difference between these gives the blood volume ejected in each heart beat (SV) and the ratio of SV to EDV gives the ejection fraction (EF). These parameters give the performance of the heart as a pump and provide a sensitive measure for heart failure.

Vascular perfusion can be measured by injecting a bolus of contrast agent which on the first pass measurements can illustrate volumes of ischemic tissue. The contrast agent rapidly washes out of healthy tissue, but slowly accumulates in infarcted regions and is retained in this tissue. Late gadolinium enhancement (LGE) imaging (about 15 minutes post bolus injection) provides a measure of the infarcted region and this region compares well with direct histological measures of infarcted tissue. Displacement encoding with stimulated echoes (DENSE) is an MRI technique that evaluate muscular performance throughout the left ventricle by measuring the motion of the myocardium, muscular stress and contractility. PET imaging using the glucose analogue, 18F-fluorodeoxyglucose (FDG) indicates cardiac metabolism and as a result is a measure of cell viability.

A University of Cambridge group studied mice whose left anterior descending coronary artery (LAD) was occluded for 30 minutes to induce an ischemic insult with imaging being performed following 24h of reperfusion[8]. The imaging sequence involved using MRI followed by PET imaging with co-registration performed retrospectively.

Cine MRI provided information on cardiac function with LGE MRI demonstrating the region of the heart which became infarcted as a result of the vessel occlusion. DENSE MRI images showed that the necrotic area and the tissue immediately close to the infarct had a reduced displacement. Displacement images were

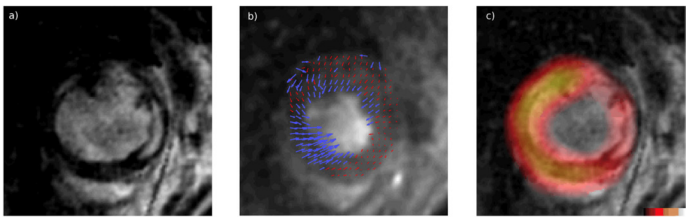

Figure 6. From Buonincontria, et. al. 2014[9] One short-axis slice from a single mouse. a) End diastolic LGE image, areas of hyperenhancement correspond to non-viable tissue. b) End systolic DENSE-derived Displacement map: a hypokinetic area (marked in red) is present larger than the infarct. c)End diastolic FDG-PET uptake is reduced in the infarcted areas, although small infarcts are not visualised in the PET image.

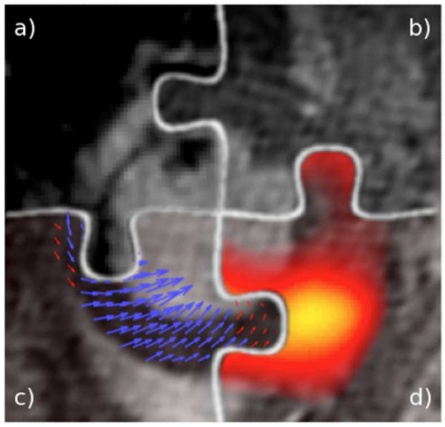

Figure 7. From Buonincontria, et. al. 2014[9] Complementary information from multi-modality imaging can provide an accurate assessment of different aspects of a myocardial infarction: a) LGE MRI shows non-viable tissue. b) Cine MRI evaluates global heart function. c) DENSE MRI interrogates local muscle performance and d) PET is used for cell viability by monitoring metabolism.

processed to obtain radial and circumferential strains. As shown in Figure 6, regions of reduced displacement corresponded to areas with increased circumferential strain, indicating passive contraction.

Cine MRI, LGE MRI, DENSE MRI and FDG PET were for the first time obtained in a single session. As shown below, each of these provides complementary information about heart disease and treatment to give a fuller picture of the heart's response to therapy.

While feasible, the demonstrated imaging protocol involves sequential imaging, inducing anesthetic stress in the animals. To minimize motion and registration error the animal transport step between scans must be managed with care. The authors noted that "the protocol would benefit substantially from simultaneity of PET and MRI". Since the protocol consisted nearly of equal parts PET and MRI, imaging time could be cut nearly in half, increasing throughput and reducing anesthesia effects and the potential for animal mortality. Paired PET and MRI data points and an overlapping, shared field of view would certainly improve co-registration and facilitate motion- and partial-volume-corrected PET reconstructions. Lastly, simultaneous acquisition could reduce experimental noise by eliminating the effects of rapid physiological and pathophysiological changes between scans.

Simultaneous PET/MRI in vivo imaging represents a robust, non-invasive and translational approach for assessing efficacy of novel treatments for MI and other cardiovascular diseases.

CONCLUSION

There is great potential for simultaneous PET/MRI imaging techniques to equip preclinical researchers with a rich set of complimentary biomarkers obtained with more control over physiological conditions. With continued adoption of human PET/MRI systems and continued research into the role for the technology in the clinic, the availability of small animal simultaneous PET/MRI instrumentation can provide a powerful platform for developing new diagnostic and therapeutic strategies in preclinical models and translating them to patients with consistent imaging protocols.

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CUBRESA
Molecular Imaging Solutions

Cubresa, Inc.
801 Berry Street
Winnipeg, MB R3H 0S7
Canada
T: +1 (204) 272-2409
E: info@cubresa.com