# Simultaneous fPET and fMRI for Assessing Dynamic Neurovascular and Neurometabolic Changes

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**Target Audience** Neuroimaging scientists, neurophysiologists.

**Purpose** BOLD fMRI has been used extensively in neuroscience research. However, BOLD fMRI probes neural activity indirectly and the signal reflects a composite change of neurovascular (hemodynamic responses) and neurometabolic (aerobic or anaerobic glucose metabolism) coupling. Neuronal activations primarily engage oxidative phosphorylation are more difficult to be detected by BOLD fMRI[1,2,3] than those involve more glycolysis if the same amount of glucoses are being consumed. Therefore, it has been suggested that measurements of hemodynamics and oxygen and glucose consumptions are required to better interpret function responses in tasks and diseases[1,2,3]. Conventional FDG PET studies can only infer changes in glucose utilization by state-contrast experiments and did not measure metabolism in a truly dynamic manner. In this study, we reinvent the use FDG PET by controlling the delivery of radiotracer to enable a truly *dynamic* detection of glucose metabolism, a technique we termed functional PET (fPET). In conjunction with simultaneously acquired BOLD/CBF fMRI, a wealth of information was obtained in one scan. Our novel imaging approach enables a more complete view to interpret changes in brain function than by using either FDG PET or BOLD fMRI alone. We first develop the imaging methods and then carry out simultaneous fPET/fMRI scans under different physiological conditions to validate our approaches.

**Methods** Dynamic PET and MRI scans were performed on three baboons (2M/1F, 14.1±2.1 kg). Animals were anesthetized with isoflurane (1%) and mechanically ventilated. Physiological parameters were monitored continuously and maintained within normal ranges. All images were acquired on a 3T Siemens TIM-Trio with a BrainPET insert and a custom PET-compatible 8-channel array coil. About 5 mCi of [$^{18}$F]FDG was continuously infused at a rate of 0.01 mL/sec intravenously for each study. PET data were stored in list mode and binned into 1-min frames. Dual echo pseudo-continuous arterial spin labeling (pCASL) data was acquired simultaneously (TR/TE1/TE2 = 4000/12/30ms, 2.2 x 2.2 x 4 mm)[4]. During an 100 min of dynamic fPET/fMRI scan, a hypercapnic challenge (7% $CO_2$) was given for 10 min and two varying concentrations of isoflurane (1.5% and 2.0%) were also given for 15 min each. Break time was provided (10-20 min) between challenges to allow animal physiology to return to baseline condition. All data was motion and slice-time corrected, skull stripped, spatially smoothed and registered to a standard NHP atlas[5]. Percent changes in BOLD/CBF and quantitative CBF maps were calculated[4]. Because an irreversible two-tissue compartmental model best describes FDG update and utilization, therefore, the *slope* of the PET time activity curve (TAC) is proportional to cerebral metabolic rate of glucose ($CMR_{glu}$). By performing a pair-wise subtraction on dynamic PET data, changes in slopes of the PET TACs can be derived into a time-series reflecting dynamic changes in $CMR_{glu}$ throughout the imaging session.

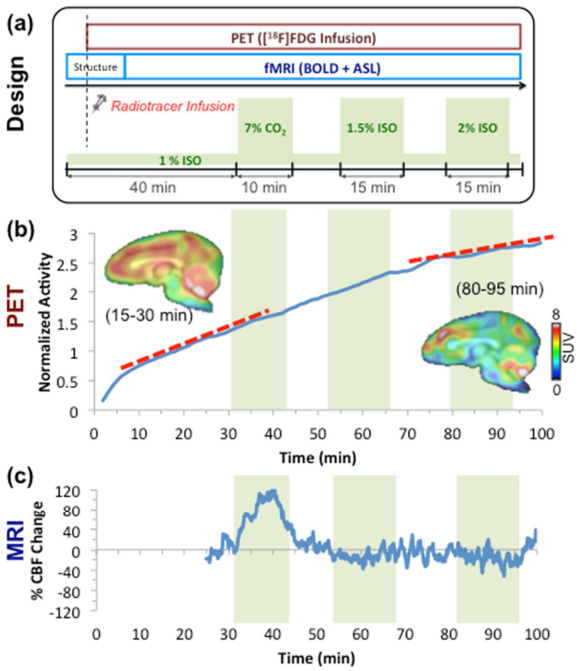


**Figure 1. (a)** Experimental design and imaging protocols. **(b)** PET time activity curve and the standard uptake value maps under 1% (left) and 2% (right) isoflurane. (c) Time course of %CBF changes.

**Results and Discussion** **Fig 1a** shows our experimental design and imaging protocols. Mild hypercapnia induced an ~8 mmHg increase in $ETCO_2$, but different levels of anesthesia did not modulate physiology significantly. **Fig 1b** represents the PET TAC from the grey matter. Increases in the level of isoflurane will decrease glucose metabolism. As expected, the *slope* of the PET TAC during the period of 2% isoflurane decreased when compare to baseline (1% isoflurane) condition (**Fig 1b**, red dash lines), suggesting a decrease in glucose metabolism. PET standard uptake value (SUV) maps also show a global decrease in FDG uptakes when comparing 2% and 1% isoflurane (**Fig 1b**, brain color insets). SUV changes are larger in the subcortical areas than cortical regions and cerebellum. Simultaneously obtained BOLD/ASL data (**Fig 1c**) demonstrated robust signal changes in responses to hypercapnia (~2.5-3% BOLD and ~90% CBF), 1.5% (~<1% BOLD and ~8% CBF), and 2.0% (~0.8-1.2% BOLD and ~20% CBF) isoflurane. It is important to note that change in CBF during hypercapnia did not affect FDG uptake, indicating that our radiotracer infusion protocol is not compromised by flow effects. This is important for future potential functional neuroimaging studies. Group results showed a graded decrease of glucose metabolism when isoflurane concentration was increased (**Fig 2**). Glucose consumptions decreased about 35% and 70% under 1.5% and 2% isoflurane from baseline (1%), respectively.

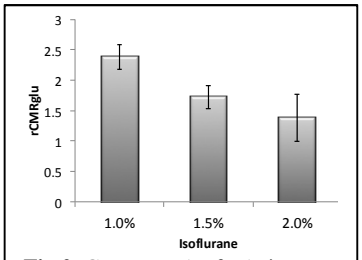


**Fig 2.** Group result of relative cerebral metabolic rate of glucose measured by fPET under different level of anesthesia (mean ± SD).

Our novel methodology confers multiple advantages. First and most important is *the ability to investigate hemodynamic responses and metabolic changes simultaneously and dynamically in one scan*. The reinvented use of FDG PET transforms it into a more attractive technique for functional neuroimaging. Our imaging protocol also allows estimation of changes in cerebral metabolic rate of oxygen using calibrated fMRI[6]. In addition, a similar GLM analysis approach commonly used for fMRI can also be applied for fPET. Since fMRI has been used extensively in neuroscience research, a fundamental understanding of how neurovascular and neurometabolic coupling results in fMRI signal will benefit the neuroimaging community.

**Conclusions** In this study, we demonstrated the feasibility of performing *dynamic fPET and fMRI* studies to reveal changes in neurovascular and neurometabolic coupling in response to physiological challenges in one scan. Our novel approaches enable a new tool for neuroscience research. Work is on-going to validate $CMR_{glu}$ quantification using fPET and to examine neurovascular and neurometabolic coupling in response to physiological and pharmacological challenges.

**References:** 1. Fox P.T., et al., Science, 1988. 2. Buzsaki G., et al., Neuron, 2007. 3. Raichle and Mintun, Ann. Rev. Neurosci., 2006. 4. Wey HY, et al., JCBFM, 2011. 5. Mclaren D.G., NeuroImage, 2009. 6. Davis T.L., et al., PNAS, 1998.